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SELECTED NON-CARCINOGENIC EFFECTS
OF
INDUSTRIAL EXPOSURE TO INORGANIC ARSENIC

October 1977
FINAL REPORT

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16. ABSTRACT

In June 1976, a study team representing four Universities and a research institution carried out a study of possible neurological effects of long-term exposure to airborne arsenic trioxide in a Western copper smelter. The study involved comparing active working men heavily exposed to arsenic in the work force with workers not so exposed. Its purpose was to determine whether nerve conduction velocity can be utilized as a biological indicator of the subtle health effects of chronic exposure to inorganic arsenic in a community setting.

The double-blind electrophysiologic and clinical study was based on 111 volunteers recruited from a selected set of smelter workers with at least five years of high urinary arsenic levels (37 men) and five years of low urinary levels (33 men). The control population consisted of members of the same union who worked at an aluminum plant in the same city (13 men) as well as male municipal employees with no industrial exposure (28 men).

The conclusions of the study are that: (1) chronic arsenic exposure in an industrial setting affects the peripheral nervous system, and (2) the neurologic parameters used in this study appear to be suitable for use in screening a community population for changes related to arsenical neuropathies.

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Abstract

In June 1976, a study team representing four Universities and a research institution carried out a study of possible neurological effects of long-term exposure to airborne arsenic trioxide in a Western copper smelter. The study involved comparing active working men heavily exposed to arsenic in the work force with workers not so exposed. Its purpose was to determine whether nerve conduction velocity can be utilized as a biological indicator of the subtle health effects of chronic exposure to inorganic arsenic in a community setting.

The double-blind electrophysiologic and clinical study was based on 111 volunteers recruited from a selected set of smelter workers with at least five years of high urinary arsenic levels (37 men) and five years of low urinary levels (33 men). The control population consisted of members of the same union who worked at an aluminum plant in the same city (13 men) as well as male municipal employees with no industrial exposure (28 men).

Demographic and other characteristics, including smoking, were obtained through use of a pre-tested questionnaire. The parameters studied included clinical examination (history and neurologic examination) and electrophysiologic tests of the sensory and motor nerve conduction in the upper and lower limbs. Levels of arsenic and eight other metals were measured in the blood, hair, urine and nail specimens collected. The study team screened the workers' blood for carboxyhemoglobin levels, diabetes mellitus and anemia. The neurological status of the men was categorized both on the clinical judgement of the examining neurologist and the objective measurements from the electrophysiologic examination. Care was taken in the analysis not to confuse age effects with other effects.

After the study population was classified into clinical neuropathy, sub-clinical neuropathy, and normal categories, a statistically significant association was demonstrated with the sum of the logarithms of arsenic levels in urine, hair and nails. This association remained after adjustment for smoking, "excuses" and average age differences in the three categories.

The conclusions of the study are that: (1) chronic arsenic exposure in an industrial setting affects the peripheral nervous system, and (2) the neurologic parameters used in this study appear to be suitable for use in screening a community population for changes related to arsenical neuropathies.

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Selected Non-Carcinogenic Effects of Industrial Exposure to Inorganic Arsenic

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Introduction

Within the past decade, scientists have come to accept the preeminent role of the workplace as well as the non-occupational environment in the induction of cancer. Accordingly, while attention has been focused in large measure on new chemicals and compounds, attempts have been made to review and update knowledge on common substances. One of these is arsenic. In this report, we furnish a brief review of arsenic's carcinogenic properties emphasizing airborne arsenic, since we do not believe they are well-known. The non-carcinogenic effects of long-term exposure to atmospheric arsenic are virtually unknown at this time though relevant information is available from episodes of arsenic-contaminated water and food.

Arsenic, known and used since antiquity, is one substance which is truly ubiquitous both from natural and industrial sources. A current NIOSH estimate indicates that in the United States alone 1,500,000 workers in dozens of occupations are potentially exposed to inorganic arsenic.[1] The list of arsenical compounds present in and discharged in the environment is extensive and includes both organic and inorganic compounds. According to Frost in his review of arsenic and biology, inorganic arsenicals are more toxic than the organic, and trivalent arsenic is more toxic than the pentavalent, but he also pointed out that for any such generalization exceptions can be found.[2]

Recently, we have witnessed a significant expansion of knowledge of the health effects of exposure to arsenic. This has occurred principally in the area of carcinogenesis. The advance in our state of knowledge may be seen by comparing the summary of the chapter on arsenic in Volume II of the International Agency for Research on Cancer (IARC) series with that of the National Academy of Sciences (NAS). The IARC is an agency of the World Health Organization (WHO).

As recently as 1973, the IARC said: "The available studies point consistently to a causal relationship between skin cancer and heavy exposure to inorganic arsenic in drugs, in drinking-water with a high arsenic content, or in the occupational environment. The risk of lung cancer is clearly increased in certain smelter workers who inhale high levels of arsenic trioxide. However, the causative role of arsenic is uncertain, since the influence of other constituents of the working atmosphere cannot be determined. An increased relative frequency of deaths from lung cancer has been found in other occupational groups exposed to high levels of inorganic arsenic compounds (e.g., sheep-dip workers, certain mining and vineyard workers). Cases of lung cancer occurring after the medicinal use of inorganic compounds, and of liver haemangioendothelioma following various kinds of exposure to arsenic have been reported, but these may be chance associations. No evidence exists that other forms of cancer occur excessively with heavy arsenic exposure."[3]

The NAS document stated: "There is some evidence that arsenicals can be mutagenic in humans. There is strong epidemiologic evidence that inorganic arsenic is a skin and lung carcinogen in man."[4]

So, in a period of a few years, we have progressed from a statement indicating that the main effect of exposure to arsenic was an increase in skin cancer to a statement that says there is strong epidemiological evidence that inorganic arsenic is a skin and lung carcinogen to man.

In every case, each of the epidemiologic studies reviewed in the NAS report (or in the critique on it)[5] has valid limitations per se. Taken together, however, they demonstrate that occupational exposure to inorganic arsenicals is carcinogenic in two different human tissues.

There is some evidence at hand of excess cancer in another human tissue. The recent study performed by Baetjer et al., compared the mortality experience of pesticide plant retirees with that of the general population of Baltimore, Maryland, the location of the pesticide facility.[6] Baetjer found even greater differences between observed and expected deaths from all cancer, as well as respiratory and leukemia-lymphatic cancer.

Unfortunately, our knowledge of the non-carcino-

genic effects of chronic exposure to airborne arsenic today is much more limited. Yet, significant information about the effects of the use of arsenical inductions and high arsenic food and drink is at hand. In the NAS report, the effect of exposure to inorganic arsenic contamination of food has been thoroughly described. Reynolds in 1901 reported the clinical expression of toxicity among 500 people consuming beer contaminated with arsenic.[9] Initial symptoms were digestive disturbances. Complaints of conjuctivitis, rhinitis, laryngitis, bronchitis and skin eruptions followed. Nervous system involvement appeared before classical skin lesions and effects on the heart and blood capillary changes were also noted. Implications of depressed immunological capacity are suggested by Reynold's observations on herpes zoster. The findings of Mizuta *et al.* reporting on accidential poisoning of individuals using contaminated soy sauce, confirm Reynold's neurological findings.[8]

The health impact of chronic community exposure to arsenic water has been addressed through studies conducted in areas where geological pecularities have created elevated levels of arsenic in the drinking water used for a protracted period of time by the inhabitants. The findings are striking in that many diseases similar to those found in occupational exposure, were found involving skin changes and skin cancer. Bronchopulmonary involvement parallels the findings with medicinal arsenic.

In 1967, Tseng *et al.* reported on a survey of 40,421 inhabitants of Taiwan, where artesian water containing up to 1.8 ppm arsenic had been used as a source of drinking water for 45 years.[9] Hyperpigmentation, keratosis and skin cancer were all reported among the population as was a peripheral vascular disorder resulting in gangrene known locally as Blackfoot disease. Individuals using drinking water containing above 0.6 ppm arsenic experienced skin cancer rates approximating five times the rate for individuals of the same age and sex living in communities where the arsenic content was 0.3–0.6 ppm. In 1974 Chuang, reporting on the relationship of Blackfoot disease and arsenic levels in drinking water, presented indications that this disease manifestation had occurred in individuals consuming drinking water containing arsenic levels as low as 0.35 ppm.[10]

In 1964, Bergoglio reported on the cancer mortality experience of inhabitants of a province of Cordoba in Argentina where natural soil arsenic levels resulted in a contaminated drinking water supply.[11] Although it had long been recognized that individuals living in this area experienced a high rate of skin lesions on the palms and soles as well as skin cancer, these observers noted that increased mortality from respiratory and visceral cancer was also occurring.

In 1971, Borgono and Greiber published the results of studies for the city of Antofagasta, Chile where the inhabitants had been consuming drinking water containing 0.6–0.8 ppm arsenic for a 12 year period.[12] Comparative studies with neighboring populations revealed that persons from Antofagasta having elevated levels of arsenic in their hair experienced an increased frequency of abnormal skin pigmentation, keratosis, chronic herpes, bronchopulmonary disease, chronic cough, abdominal pain, and chronic diarrhea, as well as cardiovascular manifestations including Raynaud syndrome, and acrocyanosis. One striking finding was the incidence of vascular disease and repeated episodes of pneumonia with bronchiectasis in children. Children may respond differently to arsenic exposure than adults.

Another recent drinking water study was that conducted in Yellowknife, Northwest Territory, Canada.[13] There did not appear to be a striking increase in the incidence of skin cancer. However, the report stated: "A comparatively large number of skin lesions were found on examination. These were notable for the number of cases of psoriasis, scaly dermatitic changes, eczematous dermatitis and a number of rashes around the naso-labial folds." It also said that clinical examination uncovered a large number of neurological findings. These neurological findings include "demonstrable loss of sensation, weakness, etc., and only exclude cases of simple "Tremor" when unaccompanied by other findings." The number appeared to be excessive but their significance could not be appraised as no control population was available. We should also like to point to the toxicologic work on chronoxie by Rozenshtein reported in 1969, as an example of the limited research on the neurological properties of arsenic.[14]

In order to shed some additional light on this issue, we undertook a study of possible neurologic effects resulting from exposure to arsenic trioxide in June 1976. In addition, the May 1977 Interim Report of the Canadian Public Health Association Task Force on Arsenic made reference to the possible need for "other areas of medical surveillance of workers."[15]

Selection of Study Site and Study Protocol

A significant point source has been identified in the continuing dissemination of arsenic in the environment, namely a copper smelter using high arsenic ores. However, while the carcinogenic effects on retired workers at the smelter have been demonstrated,[16] no similar data are as yet available on the morbidity patterns of the community residents though the burden of arsenic as measured in urine and hair has been found to be elevated.[17] The stigmata of high arsenic exposure such as dermatitis, perforation of the nasal septum, conjunctivitis, pigmentation and keratosis have not been reported in the community thus far despite newspaper and other publicity given to the emissions of arsenic from its smelter. Accordingly, it appeared necessary to rely on a subtle measure of possible neurological damage.

This measure, the peroneal nerve conduction velocity test, had been performed on children age 5 to 9 exposed to lead in Kellogg, Idaho, with measurable differences indicated between highly lead-exposed and less exposed children.[18] We believed that the finding of altered nerve impulse conduction velocity (NICV) in confirmed cases of arsenical exposure would be an important documentation of possible adverse effect on the nervous system in such individuals.

In 1975, we approached a group of faculty members at the School of Public Health and Community Medicine, University of Washington about their interest and ability to carry out a study of the hazards arising from the Tacoma Smelter of the American Smelting and Refining Company (ASARCO) to the health of residents of Pierce and King Counties. The community study would involve sampling of a stratified random sample of clusters of households in the two counties, and would also involve measurement of arsenic (and possibly other metals) in tissues of residents of these households and in the immediate environment of their residence in soil, air, dust, etc. A subsample of this group of residents identified by questionnaire responses as having symptoms or health conditions potentially ascribable to the exposure to arsenic were to be invited to have a careful physical examination by a physician trained to look for adverse manifestations of arsenic exposures. Among the possible health effects of arsenic exposure to be looked for was reduced nerve conduction velocity, an effect known to be associated with relatively heavy exposure to lead.

Before undertaking an extensive epidemiologic study of the exposed community population it was decided that a limited study of workers should be done, including some with exposures higher than those of the general population, in order to determine if NIVC was adversely affected by arsenic exposure and if the technique were sensitive enough to reveal changes in the exposed public. Accordingly, the same faculty group was thus asked to plan a pilot study involving working men from the Tacoma Smelter and a comparison group of working men not exposed to arsenic in their workplace.

Through the cooperation of the management of the Tacoma Smelter, the union representing its and other employees and officials of the City of Tacoma, we proposed a plan with the following general outline. ASARCO would furnish rosters of approximately thirty men in each of two categories: men working in plant locations where the arsenic exposure was high and roughly comparable men whose exposure was known to be low. A third group of men for comparison would be sought from members of the same union employed at an aluminum plant in an area in which no arsenic exposure existed. This third group was ultimately expanded to include men employed by the City of Tacoma in non-industrial settings.

Each volunteer from these groups was to have his nerve conduction velocity tested for one or more nerves and provide samples of blood, urine, hair and nails for laboratory determination of content of arsenic (and other metals). The resulting data were to be analyzed to determine the association (if any) of increased levels of arsenic in the tissues studied and reduced nerve conduction velocity. This study as stated previously, was conducted in June of 1976.

An account of the study and the findings of the resulting analyses constitute the substance of this report. Selected sections of the report depend entirely upon the contribution made to the study by two groups subsequently separately contracted to do the neurological investigation and the laboratory determinations; the neurological group headed by Robert G. Feldman, M.D., Chairman of the Department of Neurology, Boston University, and the laboratory team headed by Guy J. Goble, Ph.D., Department of Environmental Health, University of Washington. The data processing and the preliminary statistical analysis, as well as the supervision of the field word, were the responsibility of Professor Donovan J. Thompson and colleagues from the Department of Biostatistics, University of Washington. Additional and more detailed statistical analysis were the responsibility of Professor Wilfrid J. Dixon and members of his staff from the Department of Biomathematics, University of California at Los Angeles. Phillip Enterline, Ph.D. of the University of Pittsburgh was responsible for the work history records used in the study.

FIELD WORK

Study Subjects

From preliminary meetings with representatives of the plant management and the union local, it was agreed that a group of approximately thirty men employed in areas of the smelter with high exposure to arsenic would be identified. These men and a comparison group of about the same size, matched as nearly on age as possible, would be invited to participate. Subsequently, the high exposure group was further defined to be men who had had urinary arsenic levels of 200 ug/liter or more for at least the past 5 years. Later, the management agreed to increase the roster to fifty men in each category from which 37 and 33 volunteered to participate, respectively.

In an attempt to ensure a comparison group with no exposure to arsenic in the workplace, which yet would have comparable other characteristics, efforts were made to enlist volunteers from members of the same union that represent the ASARCO employees who worked at an aluminum plant in Tacoma. When a sufficient number of volunteers from this source appeared to be unlikely, an appeal for support was made to officials of the City of Tacoma to canvass their male employees with no industrial experience for volunteers for the study. The two sources ultimately furnished 13 and 28 participants, respectively. The total study group thus consisted of 70 men from ASARCO and 41 non-ASARCO men. An additional 6 persons participated in the study for various reasons (5 males and 1 female) but have been excluded from most analyses, since they were not recruited from the groups to be compared (the study Director, an interested professor-observer, two EPA observers, the study interviewer, a son of a planned participant who could not attend due to illness). Men volunteering to participate were furnished transportation to and from the study site and paid $10 for their effort.

Study Facility and Procedures

The study was conducted on June 9, 10 and 11, at a convenient central location, the Tacoma Labor Center in downtown Tacoma. Figure 1 in the Appendix is a sketch of the study space provided in this air conditioned, mod-

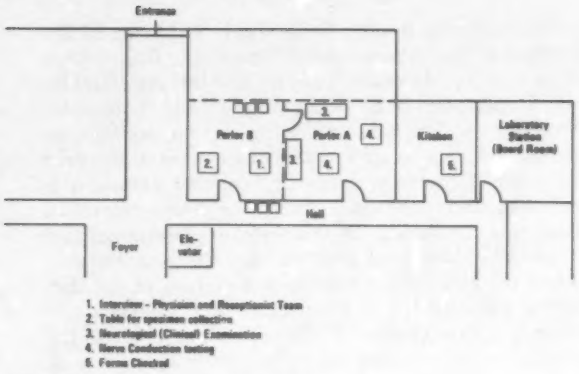


FIGURE 1. Layout of Study Space

ern facility. Men were scheduled for their appointments in a manner that ensured that ASARCO men were thoroughly intermingled with men from the other two sources during each portion of the two study days. A participant upon arrival was seated in the hall near Parlor B until study personnel were ready to start him through the routinized study procedures. Upon entering Parlor B a receptionist-physician team interviewed the participant using the questionnaire appended (Appendix A) and accepted the urine specimen he brought with him. This specimen was from the first voiding upon arising in the morning for most of the participants. A few participants not on the day shift brought specimens obtained at other times. Following the interview, the participant was asked to disrobe to the waist and remove his shoes and stockings. He next was sent to a station where a nurse took samples of his toe and finger nails (approximately 100 mg.) and a swatch of hair from the back of his head (approximately 50 mg.). Each participant carried with him a sheet of computer labels with his identification number printed on each, one of which was affixed to his questionnaire, his urine specimen bottle, and to each subsequent specimen or form pertaining to him. Next, a blood specimen of 25 cc's was drawn by a second nurse. Three vacutainers were obtained for each man: 10 cc's for metal determinations; 10 cc's for the SMA-18 battery and 5 cc's for carboxyhemoglobin and hematocrit determinations. Each container was labelled and taken to the laboratory station (Board Room) where the bloods were refrigerated and transported regularly, either to the laboratory of Tacoma General Hospital (within a mile of the study site) for the SMA-18 studies, or to the laboratory at the Department of Environmental Health, University of Washington, Seattle, for determination of content of the nine metals under investigation: antimony, arsenic, cadmium, copper, lead, mercury, nickel, selenium and zinc. Hematocrit determinations and specific gravity of the urine specimens were made immediately by the laboratory team in the Board Room.

Neurological Studies

The neurological examination and the nerve conduction testing were conducted in Parlor A. To insure the blinding of the place of employment, all volunteers were asked not to mention where they worked during the examination. Moreover, there was no indication on any of the appointment rosters as to whether the man came from ASARCO, the aluminum company, or the City of Tacoma. Scheduling, as mentioned, interspersed men from the three locations and was not discussed with the neurologist. Men appeared for the examination in their street clothes, barefoot and stripped to the waist. Two neurologists alternated in conducting the clinical neurologic examination. Again, to eliminate the possibility of the clinical examination influencing the determination of the nerve conduction velocities, the neurologist conducting the clinical examination influencing the determination of the nerve conduction velocities, the neurologist conducting the clinical examination did not assist in the electrical studies for that man. Inadvertent information (if any) acquired during the clinical examination through conversation with the men could therefore not influence the velocity or amplitude measurements. During the nerve conduction testing no conversation between physician, technicians and the volunteers took place. From observation of the entire procedure the blinding seemed to be secure. The results of the clinical examination were recorded on a standard neurological form (Appendix B). A history of metabolic disturbances, nutritional disturbances, trauma, alcohol consumption and medication was obtained and then a full neurological examination was carried out.

When the clinical examination was completed the participant passed to the nerve conduction testing station near the exit door in Parlor A.

For the electrophysiological examination, sensory and/or motor nerve conduction studies were carried out on the following nerves: 1) the right ulnar nerve-sensory/motor 2) the right common peroneal nerve-motor; and 3) the right sural nerve-sensory. Both conductions and amplitudes were measured for each nerve using standard techniques, with surface electrodes.[19-22]

Two electromyographs (Teca 4), each equipped with a digital averager, were used for the study. A supramaximal stimulus was delivered on each occasion with a duration of 0.1–0.2 millisec. and a potential of 100-300 V. The sensory action potentials for both the ulnar and sural nerves were averaged 32 times in every case. The room temperature was kept at 74-75° F for all recording sessions. In addition, surface skin temperature was also monitored in every case throughout the study, using a specially adapted telethermometer, manufactured by the Yellow Springs Instrument Company. The skin temperature was maintained at an average of 33° C.

At the completion of the electrophysical examination, the participant dressed, reported with his completed forms to the kitchen where the completeness of all materials relating to the study was checked. Payment for his participation occurred at this time and transportation back to work or home was offered.

On the first day of the study, participants were asked if they would volunteer for a repeat nerve conduction testing session on the following day. This invitation was offered systematically to each participant until ten volun-

teers had been identified. These men returned on Friday, June 3, and were worked into the schedule for nerve conduction testing only. The test re-test results are presented later in this report.

The field work was completed on schedule on Friday afternoon, June 11, without incident.

LABORATORY PROCEDURES AND DATA PREPARATION

Laboratory Procedures

One vacutainer containing 10 cc's of blood for each participant was used for the SMA-18 battery which was run in the laboratory of Tacoma General Hospital. The results for this battery were reported on the appended from (Appendix C). These data were edited, key punched, and entered into the GA-16 computer of the Department of Biostatistics, University of Washington.

The other bloods, the urine sample, and the hair and nail samples were processed by the laboratory of the Department of Environmental Health, University of Washington. A brief description of their procedures follows:

Cleaning of Glassware

Urine specimen bottles were thoroughly washed and rinsed then given a final rinse with purified nitric acid. This final rinse was poured out and the bottle stoppered.

Blood specimens were collected in tubes which were certified free of heavy metals, while hair and nails were collected in plastic bags.

Cleaning of Samples

Nails and hair were weighed into a clean digestion vessel. These specimens were washed with a 1% Triton X-100 solution and placed in an ultrasonic bath for 10 minutes.[24-28] These were then rinsed twice with distilled water and drained.

Digestion

Specimens were digested for mercury analysis by heating with concentrated sulfuric acid at 50-60°C for 30 minutes.[29] These were then soaked overnight with 6% potassium permanganate. The samples were taken to volume with 1% nitric acid.

Blood, urine, hair and nails used in the analysis of the remaining metals were digested with 0.1% sulfuric acid or perchloric acid at 50-60°C for 30 minutes.[27] These were then soaked overnight with 6% potassium permanganate. The samples were taken to volume with 1% nitric acid.

Extraction

This technique was applied to blood and urine specimens for the analysis of nickel, antimony, selenium, cadmium, zinc and lead.[29-29] The digestates were adjusted to pH 2.7 with 10% NH^4OH and extracted with 0.4% ammonium pyrrolidine dithicarbamate (APDC) in 10 ml of methyl isobutyl ketone (MIBK).

Analytical Methods

A. Arsenic in Blood and Urine[30]

The acidified digestate was treated with sodium borohydride, the liberated arsine gas was swept with argon into the heated graphite furnace of the Atomic Absorption Spectometer (AAS).

B. Arsenic in Hair and Urine[31-32]

A 10:1 aliquot of the digestate was pipetted into the graphite furnace for ASS analysis.

C. Mercury in all substrates[33]

A aliquot of the digestate was neutralized with 20% hydroxylamine, then treated with 1.0 ml of 20% stannous chloride. The reduced mercury was swept into a quartz ended cell with a 1350 ml/min air flow and measured by cold vapor technique in AAS.

D. Nickel, Antimony, Selenium, Cadmium, Zinc, and Lead in Blood and Urine[31-32]

A volume of 10:1 of APDC chelate in MIBK was pipetted into the graphite furnace for AAS analysis.

E. Zinc and Copper in Hair and Nails

The final digestate was aspirated into a flame for AAS analysis.

Quality Control

A. Blind Controls[34]

Ten percent of all samples were split into multiple samples and assayed as separate samples, not known to the laboratory technician.

B. Reagent Blanks[34]

Two percent of all analytical samples were distilled water and treated in all respects (digestion, extraction, etc.) as if they were regular samples. These samples might be spiked with appropriate metals.

C. Standard Curves.

Working standards were prepared fresh daily and results compared to an existing analytical concentration: Absorbancy curve. Results must be within a standard deviation of each working standard before analyses can proceed.

D Analysis.

Standard curves were prepared in duplicate at the beginning of each metal: substrate set and at the beginning of each day; these were compared to the working curve. Samples were run in groups of ten, the tenth specimen was assayed twice, an appropriate level standard was also run at this time. Standard curves were repeated at the end of the working day and at the end of a metal: substrate set.

E. Data Reduction.

Instrument noise levels were determined, twice this value was used to calculate the minimum detectable level from the regression line curve. The metal concentration of substrate was determined by substracting the reagent blank from the concentration as derived peak height reading.

All calculations were rechecked by a disinterested party to minimize the likelihood of errors. For each metal: substrate set the precision for both the blind duplicates and sample replicates have been summarized and are presented in Appendix D.

A summary of the "normal values" for the various metal: substrate combinations gleaned from a search of the literature together with the mean ± two standard deviations is reported in Appendix E. Additional data regarding the laboratory procedures and quality control efforts of the laboratory director are also included as Appendix F.

Data Preparation

The questionnaire results for each participant were coded and entered into the G.A. Computer. The neurological examination resulted in each participant being classified as normal, having a sensory neuropathy, a motor neuropathy or both a sensory and motor neuropathy by criteria established by the consulting Boston neurological group. A copy of their report, case by case, is included as Appendix G. Where a condition unrelated to industrial exposure was thought by the neurologist to be potentially implicated as the reason for neuropathy (or slowed nerve conduction) it was indicated on this listing. Again these data were coded and entered into the computer.

The basic nerve conduction measurements for each participant are included as Appendix H. These data also have been entered in this form into the computer. For reasons that are not clear the neurological information for two participants was lost during the processing of the material in Boston. Normal values for the electrical parameters from the experience of the consulting neurological group are included as Appendix I.

Finally, through the joint efforts of Dr. Phillip Enterline at the University of Pittsburgh School of Public Health and ASARCO officials, a set of work history records and past urinary arsenic and lead determinations were furnished for all participants from ASARCO. These records were summarized through a coding scheme that recorded for each man the years of employment in the smelter, year of first urinary arsenic determination, total number of such determinations, minimum, and average urinary arsenic value, and the maximum past urinary lead value. A copy of the basic record is appended (Appendix J-a-b).

ANALYSIS

Characteristics of Participants

In planning the study, a number of issues were raised relating either to non-industrial causes for reduced nerve conduction (or neuropathies) or the exposures (principally to arsenic) from sources other than the work place. These issues resulted in framing a series of questions included on the questionnaire and/or asked during the neurological examination.

An examination of the responses from the total group of participants can eliminate a number of these issues from further consideration. Ingestion of shellfish in the 36 hours to prior examination was reported by only 2 of the 117 participants. No participants reported taking anti-convulsants, anti-tuberculosis drugs, or medications containing arsenic. Only 2 men taking medicine for diabetes, 2 taking hormones, 3 taking thyroid medication, and 2 taking tranquilizers. As causes for any differences in either exposure to arsenic or nerve conduction abnormalities among the groups of workers to be compared these may safely be dismissed from further consideration.

Somewhat more frequent reports of other conditions occurred: 15 cases of recent trauma, 12 men on anti-hypertension medication; 15 with substantial weight loss in past three months, 7 with history of liver disease, 27 who obtain their home drinking water from wells (potentially a source of arsenic) and 13 who admitted to current gardening activity involving spraying with insecticides (again, a potential exposure to arsenic). Examinations of the distribution of these occurrences among the four worker groups revealed that there were no concentrations in a single group that would be likely to disturb the group comparisons.

Two other characteristics potentially affecting group comparisons, alcohol consumption and cigarette smoking, were far more frequently reported. Most of the participants drink alcohol (102) and 46 admitted to having consumed alcohol in the 48 hours prior to examination (despite being asked not to). Cigarettes are currently smoked by 61 of the men. Examining the distribution of men with these characteristics among the employer groups showed association of these characteristics with place of employment, a result that might have been expected.

A somewhat similar situation prevails with respect to age. Here, although the two ASARCO groups (high and low arsenic exposure) are comparable on age—an average age of 47 years in both groups with range 26-60 in the high and 22-62 in the low exposure group—they differ markedly from both of the comparison groups which average 39 years of age with a range from 22-58. Since it is also known that [the amplitude of the response to the electrical stimulus used in] the nerve conduction testing is slightly age dependent, and some evidence exists for velocities also being age dependent, this difference is troublesome in subsequent analyses. However, it may be noted here that neurological differences between the ASARCO employees and the other two groups cannot be accounted for by the age difference above, and that neurological pathology is not confined to the older workers in either the ASARCO or the comparison groups. This problem will receive further attention in subsequent sections of the report.

A final variable whose potential impact would be to narrow the average exposure to arsenic and other metals

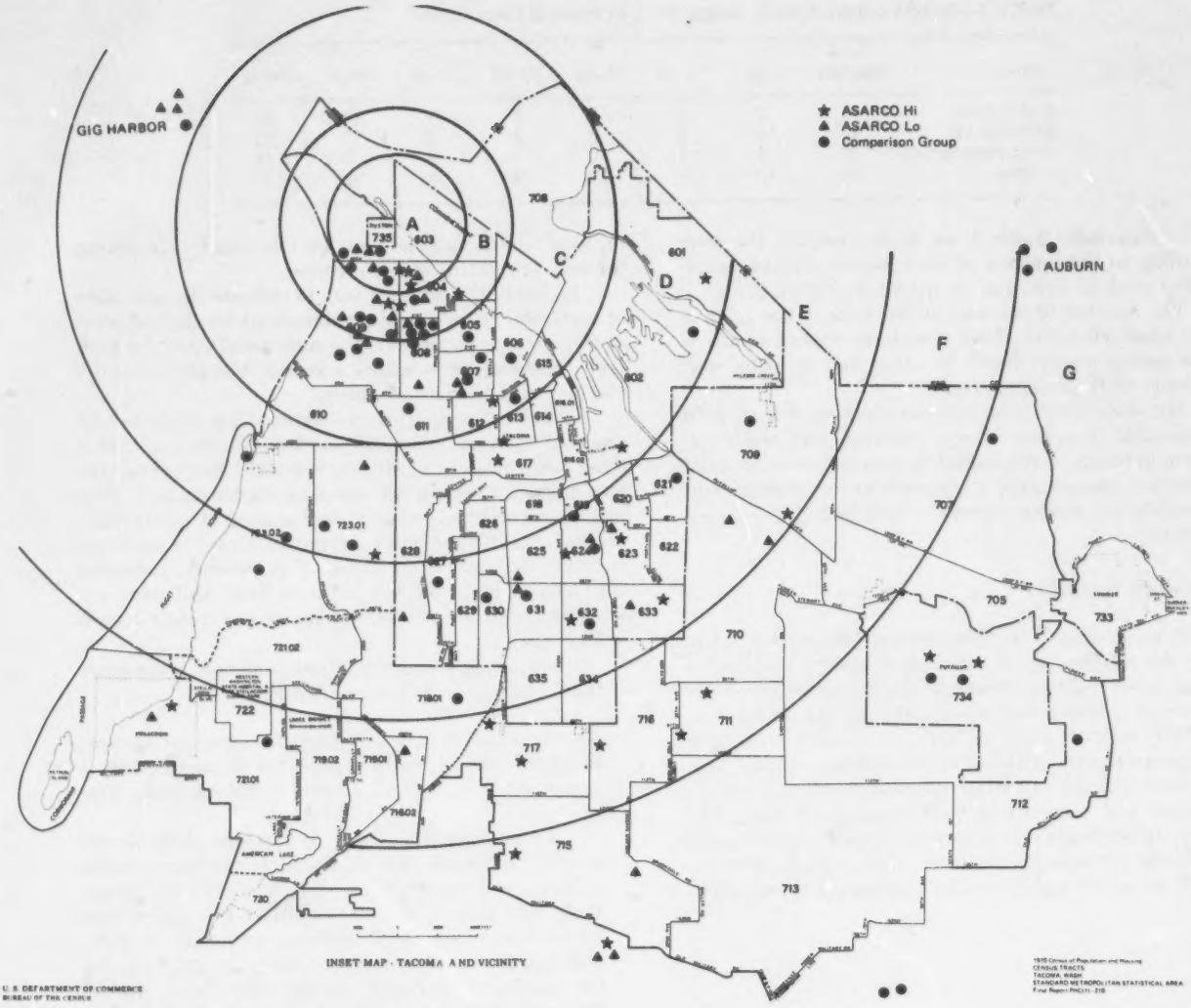


FIGURE 2. Residence Location of Study Participants

between the ASARCO employees and the comparison group, is place of residence. If the micro-environment of a person's residence were contaminated by effluent from the smelter stack, presumably this would be detectable by examining levels of arsenic in the tissues of men not exposed in their workplace, and then relating average levels in groups of men to distance and direction of their residences from the smelter stack. The role of place of residence and exposure to arsenic as measured by tissue levels has been examined. In Appendix Figure 2 the residence location of the 111 participants has been identified. The residence location of men from ASARCO Hi and ASARCO Lo groups are indicated by solid dots while those of the aluminum and Tacoma workers are open circles. Clearly, some of the comparison group men live near the smelter and may exhibit higher arsenic levels in their tissues than those living at a distance from the smelter stack.

TABLE 1—Classification of Men According to the Location of their Residence Relative to the Smelter Stack

Urinary(PPb) Arsenic	Place of Employment					
	ASARCO Hi		ASARCO Lo		Tacoma & aluminum	
Area	n	$\bar{x}$	n	$\bar{x}$	n	$\bar{x}$
A&B	12	867	9	152	8	33
C&D	9	1465	10	223	15	3
E&F	12	891	10	85	9	19
G	4	524	4	170	9	118
Hair (PPm)						
A&B	12	2380	9	76	8	9
C&D	9	1388	10	68	15	4
E&F	12	2658	10	207	9	5
G	4	719	4	108	9	5

TABLE 2—Current Urinary Arsenic Values (PPb) by Place of Employment

Group	None Detectable	<10	10-19	20-29	30-49	50-99	>100	TOTAL
ASARCO Hi	1	2	2	3	7	11	11	37
ASARCO Lo	14	6	3	7	2	0	1	33
Comparison Group	33	2	4	1	0	1	0	41
Total	48	10	9	11	9	12	12	111

In Appendix Table 1 we have classified the men according to the location of their homes relative to the smelter stack as indicated on Appendix Figure 2.

The number of the men in the cells of the table is quite small. However, there is no indication of a pattern of increasing arsenic levels in either hair or urine with proximity to the smelter stack.

The conclusion from this examination is that, with the possible exception of age, smoking, and residence, those potentially confounding factors which were valid concerns in planning the study seem not to be important in considering arsenic exposure and neurologic deficit associations.

Exposure Results

Principal interest in this study was directed at examining the relationship of exposure to arsenic and neurological abnormalities. Of necessity, the measurement of this exposure had to be limited to the present for the non-ASARCO workers since no historical records existed for this group. For the ASARCO participants, company records were utilized to obtain information on past arsenic exposure and some limited information on lead. The current information on exposure to metals was expanded to include antimony, cadmium, copper, lead, mercury, nickel, selenium and zinc. The amounts of these metals in urine, blood, hair and nails are the basis for classifying the exposure status of each worker.

Probably the simplest way to indicate the relevance of particular tissue-metal combinations for the purposes of this study is to tabulate the number of cases for each such combination in which a known non-zero quantity was recorded by the laboratory.

Clearly, if a metal-tissue combination could not be detected in more than half of the participants, and if those with positive results are scattered throughout the four employer groups with no quantitative pattern, little will be learned from more formal analysis. On this basis, no further examination of antimony, nickel or selenium in urine; the same three metals plus mercury, cadmium and arsenic in blood; selenium in hair; and mercury, selenium, cadmium, nickel, antimony and copper in nails will be made.

Since principal interest relates to arsenic, a summary of these findings will be presented first.

1. *Arsenic Exposure.* Current arsenic exposure as measured by urinary arsenic values for all participants is summarized in Appendix Table 2 and Appendix Figure 3.

   From Appendix Table 2 it seems clear, as expected, that workers with the higher urinary arsenic values are concentrated in the ASARCO Hi group. Only two men from the ASARCO Lo, and Kaiser Aluminum groups had values greater than 50 PPb; respectively, 64.2 and 167.0. The average value for the ASARCO Hi group, on the other hand, was 98 PPb with 22 of the 37 men having values greater than 50 PPb. It should also be noted that no arsenic was detected by the laboratory procedures employed in the urines of 48 of the men tested.

   Examining the urinary arsenic values from the records furnished by ASARCO, we can summarize the differences between the ASARCO Hi and ASARCO Lo groups in several ways as shown in Appendix Table 3.

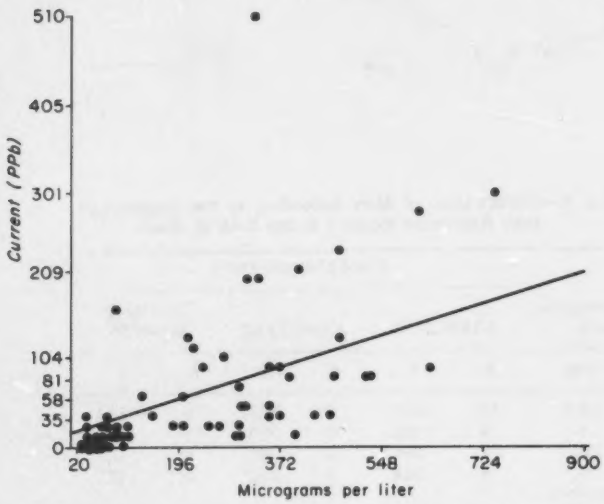


FIGURE 3. Association of Current Urinary Arsenic Values (PPb) and Average of Past Values (Micrograms per liter) for Asarco Participants.

TABLE 3—Historical Urinary Arsenic Values for ASARCO Participants

Group	Micrograms per liter			
	Average	Average of Maxima	Average of Minima	Average Years Employed
ASARCO Hi	378.5	822.2	136.1	14.5
ASARCO Lo	74.1	122.8	41.2	16.4

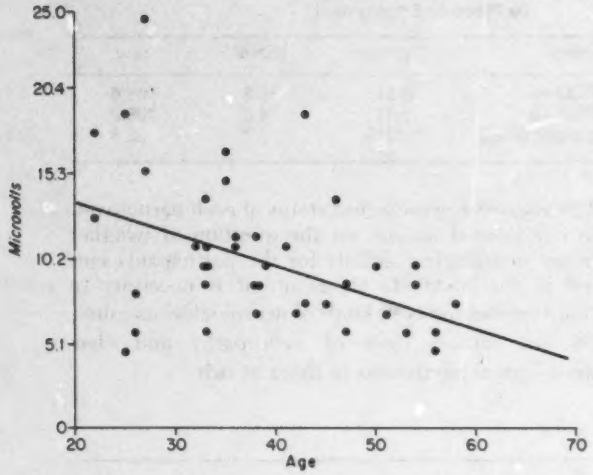


FIGURE 4. Ulnar Sensory Amplitude by Age (Control Group Only).

Again, it is clear that these two groups differ markedly in their past exposure to arsenic. Thus, we may conclude that the volunteers for the study do exhibit current and past differences in urinary arsenic values, with men having high values belonging exclusively to the ASARCO Hi group.

It is interesting to examine the correlation of the historical and current urinary arsenic values. The product-moment correlation coefficient in Appendix Figure 4 is approximately one-half. If the two obvious outliers are eliminated, this coefficient changes to .67 showing a reasonably strong association of past and current values. On the other hand, either through better protection for the men, modification of the work environment, seasonal variation or systematic laboratory differences in measuring these values, the current levels of urinary arsenic are related to past levels by the equation:

$$\text{Current Level of Urinary Arsenic} = 5.9 + 0.227\ (\text{Past Level}) \text{ of Urinary Arsenic}$$

showing an apparent marked overall reduction in exposure. Roughly speaking, current levels appear to be only 23% of former levels.

No past arsenic values are available for other than urine, so the comparison of arsenic in hair, nails and blood must be limited to the current study results. As indicated earlier, arsenic was detected by the laboratory in the bloods of only seven of the 111 men.

TABLE 4—Average Arsenic Values (PPm) in Nails and Hair by Place of Employment

Group	Nails	Hair
ASARCO Hi	72.8	182.6
ASARCO Lo	21.1	8.9
Comparison Group	1.2	0.6

TABLE 5—Current Lead Values in Urine, Blood, Hair and Nails by Place of Employment

Group	Urine (PPb)	Blood (PPb)	Hair (PPm)	Nails (PPm)
ASARCO Hi	19.8	207.9	132.9	13.0
ASARCO Lo	12.8	105.5	93.1	6.7
Comparison Group	7.8	120.2	59.4	3.1

Four of these men were in the ASARCO Hi group, two in the aluminum and one in the Tacoma group, with the highest values being 80 PPb, occurring in a man with no arsenic detectable in his urine and nails and a value of 1.0 in his hair. Thus, blood arsenic is not a useful measurement in this study. For the hair and nail samples, we have the results shown in Appendix Table 4.

Again, these results clearly distinguish the groups and add an element of exposure duration to the comparison, recognizing that an arsenic exposure today would show up in hair and nail clippings some weeks or months later.

2. *Exposure to Other Metals.*

Lead: Since lead exposures have been associated with neurological deficits in other studies, it is of interest to examine the differences among employee groups for this metal. Appendix Table 5 summarizes the findings.

The pattern of this table is high values of lead in all the four tissues for the ASARCO Hi groups; intermediate values for the ASARCO Lo; and lower values for the comparison group except for blood.

Copper: The comparison of the employer groups for the copper in urine and blood is shown in Appendix Table 6. The conclusion from the values in this table is that copper in blood and urine does not differentiate the employer groups.

The hair specimens gave quite different results, as shown in Appendix Table 7. The high recovery of copper from the hair of the ASARCO Lo group should be noted.

Other Metals: The results for the other metals in the nail specimens are shown in Appendix Table 8.

Generally, these results are typical of what is found for these metals in the other tissues; one or both of the ASARCO groups have the highest values.

A summary of the results for metals found in the tissues of the men from the four places of employment might be that one or the other or both of the ASARCO

TABLE 6—Current Copper Values (PPm) in Blood and Urine by Place of Employment

Group	Blood Averages	Urine Averages
ASARCO Hi	0.99	.072
ASARCO Lo	0.93	.054
Comparison Group	0.96	.043

TABLE 7—Current Copper Values (PPm) in Hair by Place of Employment

Group	Hair
ASARCO Hi	102.6
ASARCO Lo	94.5
Comparison Group	10.2

TABLE 8—Current Values for Cadmium, Nickel, Zinc in Nails by Place of Employment

Group	Cadmium	Nickel	Zinc
ASARCO Hi	0.51	16.6	105.6
ASARCO Lo	0.11	4.6	108.2
Comparison Group	.019	2.7	92.8

groups tended to have the highest mean values. Also, large differences between ASARCO Hi employees and the other men exist for arsenic and lead.

Neurological Findings

As described in Section II, both a clinical neurological examination and objective electrical measurement were used to assess the neurological status of each participant. Since our interest focuses on the question of whether there are neurological deficits for the participants employed in the ASARCO Hi group, it is necessary to continue to examine both kinds of neurological measurements i.e. clinical signs of neuropathy and electrophysiological parameters in those at risk.

TABLE 9—Electrical Test-Retest Results for 10 Participants

NERVE:	ULNAR								PERONEAL			SURAL	
	MOTOR						SENSORY		MOTOR			SENSORY	
	V			A					A				
Participant	Wrist-elbow	Elbow-axilla	MAP DUR	wrist	elbow	ankle	V	A	V	ankle	knee	V	A
1	57	49	13.2	7.5	7	6.5	54	14	46	8	6	42	8
	56	57	12	10	10	10	52	15	50.5	2.5	2.5	36.8	5
2	55.8	53	9.6	10	10	9.5	57.8	12	45.8	5.4	5.4	43.7	6
	52	59.5	12.5	2.4	2.4	2.2	47.5	10	48	4.8	4.4	43	18
3	58	70	13.4	13.5	12	12	52	8	44.6	2.0	2.6	43	10
	55	60	13.2	10.5	9.2	9.2	30.5	8	46.8	1.5	2	41	15
4	48	57	15.5	8.5	8.2	8.6	45	7.5	47	4.6	5.3	42	9
	58	50	13	8.5	8.5	7.5	42	5	48	4.6	6.0	36	5
5	54	66	12.9	11.5	10	10	61	12	43	4.4	3.4	45	12
	58	57	10.7	10.0	9.5	9	63	14	46	9.5	7.5	36.7	21
6	56	71	14.6	2.2	1.8	1.8	56	9	47	3.7	3	45	9
	63.5	59	12	6.5	6.7	5	70	9	48	1.8	1.2	40	9
7	62	62	12.7	5	3.4	4	55	11	50	3	3	48	18
	61	67	9	13	12.5	12	47.5	24	49	5.6	5.6	48	14
8	64	56	12.8	8.5	8.7	6.5	49	6	55	9.2	9.5	42	6
	56	59	10	5.2	4.4	4.4	55	4	52	5.6	5.2	42.5	22
9	54	64	12	8	6.5	6.5	47	13	38	3.4	2.6	41	11
	57	57	12	3	3.2	3.2	40.5	3.5	34.5	2	3.4	33.5	9
10	54	51	14.3	15.5	15.5	14.5	43	14	45	10	9.5	44	7
	61	60.5	13.9	15.5	15.5	14.5	48	8	43	8.8	7.8	42	13
avg diff	−3.1	1.6	1.3	0.5	0.1	0.5	4.2	0.6	−0.4	0.7	0.5	3.6	−3.5
avg $	4.0	5.7	1.6	3.1	3.2	3.0	8.2	4.0	1.8	2.0	1.8	3.3	5.4
average	57.0	59.3	12.5	8.7	8.2	7.8	50.8	10.4	46.3	5.0	4.8	41.8	11.4
coeff. of variation	7%	10%	12%	36%	39%	39%	16%	39%	4%	40%	38%	8%	47%

V = Velocity
A = Amplitude

TABLE 10—Revised Electrical Test-Retest Results for 10 Participants

NERVE:	ULNAR								PERONEAL MOTOR		SURAL SENSORY	
	MOTOR						SENSORY					
	V			A					A			
Participant	Wrist-elbow	Elbow-axilla	MAP DUR	wrist	elbow	axilla	V	A	V	ankle	knee	V	A
1 129	57.4	57.0	13.2	7.5	7.0	6.5	56.5	14.	45.0	3.4	2.6	44.0	8.
123	57.0	57.2	12.0	10.0	10.0	10.0	52.4	15.	43.0	2.5	2.5	40.0	5.
2 30	57.0	56.5	9.6	10.0	10.0	9.5	54.5	12.	44.5	5.4	5.4	42.5	12.
67	52.5	57.0	12.5	12.0	12.0	11.0	52.4	11.	41.4	4.8	4.6	41.3	17.
3 14	58.0	70.0	13.4	13.5	12.0	12.0	52.0	8.	44.6	2.0	2.6	43.0	10.
76	57.5	60.0	13.2	10.5	10.0	9.5	48.0	8.	43.7	3.0	3.6	41.4	15.
4 20	48.5	59.0	15.5	8.5	8.5	8.5	48.1	12.	45.5	4.8	5.4	42.5	14.
62	47.5	48.9	13.0	8.5	8.5	7.5	46.0	7.	49.5	4.6	5.0	38.0	14.
5 42	53.9	64.0	12.9	11.5	10.0	10.0	61.0	12.	43.5	4.4	5.4	45.3	12.
85	58.3	58.0	10.7	10.0	9.5	9.0	60.0	14.	42.7	9.0	7.5	38.0	20.
6 58	57.0	71.5	14.6	20.0	18.0	18.0	55.5	10.	45.0	3.6	3.2	45.2	9.
84	55.6	59.1	12.0	10.0	13.0	13.0	70.0	8.	48.9	3.2	4.0	41.3	9.
7 78	59.5	64.5	12.7	12.5	10.0	10.0	50.0	11.	50.0	3.0	3.0	48.4	18.
97	58.5	61.5	9.0	13.0	12.5	12.5	47.7	12.	49.5	5.6	5.6	48.4	28.
8 104	63.0	50.0	12.8	8.5	8.5	8.5	53.0	6.	47.5	9.5	9.5	43.7	12.
55	56.4	59.4	10.0	13.5	11.0	11.0	54.0	4.	51.5	13.5	14.0	43.7	22.
9 105	54.5	60.5	12.0	8.0	6.5	6.5	48.0	13.	39.6	3.4	3.0	41.2	11.
53	53.9	60.5	12.0	5.0	4.8	4.8	46.5	5.	39.2	5.0	5.0	35.0	9.
10 45	55.0	52.5	14.3	15.5	14.5	14.5	44.6	14.	42.0	10.0	9.5	42.5	8.
26	56.7	64.0	13.9	15.5	15.5	15.5	48.2	8.	43.0	8.8	7.8	43.8	13.
Ave. Diff.	1.0	1.1	1.2	0.8	−0.2	0.0	−0.2	2.0	−0.5	−1.0	−1.3	2.7	−3.8
Avg. $\hat{s}$	2.1	5.6	1.5	2.8	1.3	1.8	3.7	2.6	1.8	1.6	1.4	2.7	4.2
Average	55.9	59.6	12.5	11.1	10.6	10.4	52.4	10.2	45.0	5.5	5.5	42.5	13.3
Coeff. of Variation	4%	9%	12%	25%	12%	17%	7%	26%	4%	29%	26%	6%	32%

V = Velocity
A = Amplitude

1. *Electrical Measurements.* With any measurement designed to distinguish differences among groups, there is a need for some understanding of its reproducibility. In this instance, ten participants volunteered to submit to a second measurement of the electrical parameters. The results for these ten men are given in Appendix Tables 9 and 10.

Appendix Table 9 results were the first computed and were done blindly in that the identity of the pairing was unknown to the person taking the measurements on the tracing. Since varying degrees of precision in the recording were evident in the results, the neurologists agreed to recalculate the entries in the table. The result is Appendix Table 10. In this

TABLE 11—Average Nerve Conduction Velocities (Meters per Second) by Place of Employment

Group	Number	Ulnar-Motor Wrist-Elbow	Ulnar-Motor Elbow-Axilla	Ulnar Sensory	Peroneal Motor	Sural Sensory
ASARCO Hi	36	55.6	63.5	50.4	44.9	41.4
ASARCO Lo	33	54.4	63.3	50.6	44.8	41.3
Aluminium	13	56.1	61.5	52.2	47.1	43.5
Tacoma	27	53.9	62.2	49.4	47.4	41.6

TABLE 12—Average Amplitudes (μV) and Duration (ms) by Place of Employment

Group	Dur.	Ulnar Motor Ap-W	Ap-E	Ap-A	Ulnar Sensory Ap	Peroneal Amplitude Ankle	Knee	Sural Amplitude
ASARCO Hi	12.4	9.7	8.9	8.5	6.4	4.7	4.4	10.7
ASARCO Lo	12.5	9.6	9.1	8.6	8.2	4.3	3.9	12.7
Aluminum	13.3	11.0	10.7	10.3	8.4	6.9	6.6	11.4
Tacoma	12.8	10.2	9.9	9.5	10.3	5.4	5.1	10.9

case, too, the revisions for these 10 individuals were done while the data were still blind to the laboratory. Revisions for the entire study population were done in the same way.

It is difficult to summarize precisely the information about repeatability of the measurements on a participant from one day to the next day and the evidence concerning calculation errors from the tracing. The coefficients of variation suggests that the velocities are more repeatable than the amplitudes. Among the velocities, the peroneal motor nerve determination appears to be the most repeatable which fits with a priori considerations regarding source of error in the electrical measurements in that this nerve is the longest nerve studied and the error in measuring its length with a steel tape should have the smallest percentage effect.

The second calculations show perhaps a little smaller average difference and their signs are more evenly distributed, six negative and seven positive, versus ten and three on the first occasion. These facts should be borne in mind in interpreting subsequent results from the electrophysical examination of the participants.

If the calculation differences are used to estimate the error of the measuring process, an average standard deviation of approximately three meters per second for the velocity determinations results. Fortunately, the recalculations do not suggest any large average bias in the initial readings but rather suggest only residual random error; 57 of 90 non-zero first minus second reading differences were negative, with an average difference of 0.02 meters per second for the 100 differences.

Average conduction velocities by employer groups are shown in Appendix Table 11. No consistent patterns by employer group are apparent with the possible exception of the differences for the peroneal nerve. Pooling the two ASARCO groups and the two comparison groups yields a mean difference in velocity for the peroneal nerve of 2.45 meters per second. This difference is significantly different from zero at the p .005 probability level. However, the anticipated difference between the ASARCO Hi and the ASARCO Lo groups, on the assumption that a higher arsenic exposure might be associated with an increased velocity deficit was not observed.

It is also of some interest that for the velocity measurement which is most repeatable, the peroneal nerve velocity, the two ASARCO groups have standard deviations of 5.5 and 5.9, as compared to 3.2 and 3.4 for the two other groups. Two possible reasons for the increased variability in the ASARCO participants may be advanced, a greater age span in these groups and the possibility of more varied exposure that may influence these measurements.

The situation for the amplitude and duration measurements is shown in Appendix Table 12.

The ordering of each of the average values is of interest. With the exception of the sural amplitude, the two lowest values are always in the ASARCO groups. Except for the sural and the ulnar sensory amplitudes, the values for the ASARCO Hi and Lo groups are quite similar. Thus, amplitude and duration means are more consistently related to workplace than are the velocities.

Many of the values in Appendix Tables 11 and 12 appear unusual when judged against the corresponding normal values (Appendix I) from the consulting Neurological Group's experience. As an example, the average velocity for the ulnar sensory nerve for the entire group of 109 participants with this measurement is 50.4 m/s which is essentially the value given for the lower end of the normal range for this velocity, 50 m/s. Only the participants from the aluminum company have an average clearly within the normal range. Somewhat similar remarks can also be made about the sural sensory velocities. For the amplitudes, it is apparent that low values are generally present in the entire group. As an example, 58 of the 109 men tested had an amplitude measurement

TABLE 13—Clinical Neuropathies by Employer Group

Neuropathies	ASARCO Hi		ASARCO Lo		Aluminum		Tacoma		TOTAL	
None	21	57%	19	58%	8	62%	22	81%	70	64%
Sensory Only	10	27%	11	33%	5	38%	5	19%	31	28%
Motor Only	2	16%	1	9%	0		0		3	3%
Both Sensory and Motor	4		2		0		0		6	5%
TOTAL:	37	100%	33	100%	13	100%	27	100%	110	100%

TABLE 14—Clinical Neuropathies by Employer Group: Eliminating Participants with Potential Reasons for Neuropathy

Neuropathies	ASARCO Hi		ASARCO Lo		Aluminum		Tacoma		TOTAL	
None	18	55%	17	61%	7	78%	22	92%	64	68%
Sensory Only	10	30%	8	29%	2	22%	2	8%	22	23%
Motor Only	2	15%	1	10%	0		0		3	9%
Both Sensory and Motor	3		2		0		0		5	
TOTAL:	33		28		9		24		94	

less than the lower limit of the normal range (8μv) for the ulnar sensory nerve. For the benefit of readers who are interested in these phenomena, the entire estimated cumulative probability distribution, the probability density function, and a histogram with "normal value" endpoints for each of these measurements are available on request. A final note on the electrical measurements can be made, again concerning the values for the peroneal velocities. Of the twelve men who have velocities slower than the lower limit of the normal range (40 m/s), all are employed at ASARCO; six in the high exposure group and six in the low group. They range in age from a low of 32 to a high of 64 years. The failure to have a concentration of these men in the high arsenic exposure group is again puzzling, suggesting at least that a dose response mechanism is not clearly evident.

2. *Clinical Findings.* If the participants are classified by the outcome of the neurological examination as having no evidence of a neuropathy or having a sensory, a motor or both a sensory and motor neuropathy, the results are as shown in Appendix Tables 13 and 14.

   A potential reason for exhibiting a neuropathy was recorded by the neurologist during the examination; e.g., diabetes, trauma, alcohol consumption, etc. If the 16 participants with such "excuses" are removed from Appendix Table 13, a slightly different impression of the association of neuropathies with place of employment is created in Appendix Table 14. No interpretation is made of these findings at this point as a discussion of the results of the multivariate analysis is presented in a later section will include interpretation of these results.

3. *Relation of Clinical Findings and Electrical Results.* Two ways of determining whether the clinical examination and the electrical measurements are identifying the same men as those having neurological abnormalities are next examined. Since there were only three participants among the thirty-one who were classified as having a neuropathy whose neuropathy was exclusively motor, the classification in Appendix Tables 13 and 14 has been collapsed to two categories, "neuropathy" and "no neuropathy" in this comparison. Also, for economy in presentation, the ulnar motor electrical values relate only to the forearm. For this comparison, we have included all persons examined and tested who did not have an excuse listed by the neurologist for a potential neuropathy.

   From Appendix Table 15, it seems possible to conclude that there is essentially no association between the clinical classification and the electrical measurements for the two motor nerves — approximately the same proportion of each neuropathy group has the various electrical abnormalities. For the sensory nerves, on the other hand, there is a positive association between the two (the proportions of electrical abnormalities do vary by class), although it is not very strong. A statistic appropriate for measuring the degree of this association on a scale from 0 (no association) to 1 (perfect association) is the tetrachoric correlation coefficient. For calculating this statistic the electrical-classification is further collapsed to "velocity and amplitude normal" and "one or both abnormal". The degree of association measured in this way for the ulnar sensory nerve is 0.46 and for the sural sensory it is 0.27, neither very high.

TABLE 15—Comparison of Clinical Classifications and Normal Values for Electrophysical Examination

		Electrophysical Examination							
		Velocity & Amplitude Normal		Velocity Reduced		Amplitude Reduced		Both Reduced	
Nerve	Clinical Neuropathy	n	%	n	%	n	%	n	%
Peroneal Motor	Yes	19	63	2	7	7	23	2	7
	No	42	67	7	11	13	21	1	1
Ulnar Motor	Yes	25	83	2	7	3	10	0	0
	No	53	84	1	2	6	10	3	5
Ulnar Sensory	Yes	5	17	2	7	11	37	12	40
	No	26	41	13	21	16	25	8	13
Sural Sensory	Yes	19	63	5	17	4	13	2	7
	No	49	78	10	16	2	3	2	3

TABLE 16—Average Conduction Velocities (M/s) and Amplitudes (uV) for Participants Classified by Neuropathy Status

VELOCITIES Neuropathy	N	Ulnar Motor Wrist-elbow	Ulnar-Motor Elbow-Axilla	Ulnar Sensory	Peroneal Motor	Sural Sensory
None	69	55.1	63.2	51.1	46.3	42.3
Sensory Only	23	53.8	63.0	49.3	46.3	41.8
Motor Only	3	56.0	66.2	53.4	45.5	41.9
Both	5	56.1	57.2	46.9	41.0	39.1
Total	100					

AMPLITUDES Neuropathy	Dur.	Ulnar-Motor Wrist	Ulnar-Motor Elbow-Axilla		Ulnar Sensory	Peroneal Motor Ankle	Peroneal Motor Knee	Sural Sensory
None	12.9	10.0	9.5	9.3	9.1	5.0	4.7	12.6
Sensory Only	12.3	9.0	8.2	7.7	7.0	4.9	4.4	9.7
Motor Only	12.5	10.3	10.0	9.5	4.7	4.8	3.5	8.7
Both	12.9	9.9	10.0	8.6	4.8	2.7	3.3	9.2

Dur. = Duration

Attention may also be called to the fact that the proportion of participants with normal electrical values varies from a high of 84% for the ulnar motor nerve to a low of 31% for the ulnar sensory nerve. If the information for the four nerves is used simultaneously to classify a participant, only 18 of 100 men in this excuse-free group have normal values for all four nerves.

A second way of examining whether the two measurements are associated is to compute the average values of the electrical measurements for men grouped by the clinical classification. These results are included in Appendix Table 16.

Some consistent results are exhibited for the two sensory nerves measured. The "motor only" and "both" groups are apparently too small for stability of the mean results in these categories for velocities and amplitudes for the motor nerves.

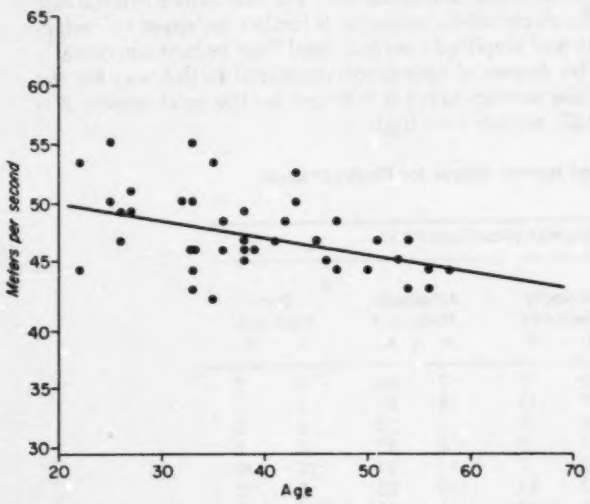


FIGURE 5. Peroneal Motor Conduction Velocity by Age (Control Group Only).

Summarizing the association between the clinical and the objective measurements of the neurological status of each man thus far, we conclude that the association exists but it is weak. In consequence, subsequent analyses of the relation of neurological deficits to exposure to various metals will either require an examination of each of the methods for describing the neurological status of a participant or the development of a new classification embodying elements of both methods.

The analyses in this section could possibly be improved if normal values specific for age were available. There is evidence in these data that both velocity and amplitude are age dependent. If anything, taken as a group, the amplitudes seem to evidence more age dependency than the velocities. If examination of the dependency on age is examined only in the non-ASARCO participants to reduce the potential confounding influences of wide variation in exposure, the results in Appendix Figures 4 and 5 are typical of the age dependency. For the ulnar sensory nerve, the reduction in amplitude for each increase of one year in age is estimated at 0.19 microvolts. The product moment correlation, r, of the amplitude with age is −0.44, indicating that only about 19% (r^2) of the variability in this amplitude is explained by age. Factors other than age, including measurement error, apparently are strongly involved in determining the outcome of the amplitude measurement. Figure 5 shows a reduction of 0.16 meters per second in the peroneal velocity for each increase of one year in age with an r = 0.48.

Neuropathy as diagnosed by the neurologist also seems to exhibit a weak association with age as shown in appendix Table 17. While the association does not reach statistical significance (p .05), the increasing frequency of neuropathy with age in the group of participants without potential excuses in quite orderly and suggestive of an age effect.

Association of Neurological Abnormalities and Exposure to Arsenic and Other Metals: A Multivariate Analysis. The descriptive data and the preliminary analy-

TABLE 17—Number and Percent of Participants with Clinical Neuropathies by Age

GROUP	AGE 20-29	30-39	40-49	50+	TOTAL
No Neuropathy	8 80%	24 77%	9 69%	22 56%	63
Neuropathy	2 20%	7 23%	4 31%	17 44%	30
TOTAL	10	31	13	39	93

sis were predominately done at the University of Washington, and have been presented above. These were supplemented by a sophisticated multivariate statistical analysis.

Since statistics moves from the simpler techniques to the more complex analyses to uncover relationships, we shall now deal with a limited multivariate analysis of the neurological responses in relation to the categorical demographic groups, arsenic levels and covariates.

As the entire pilot investigation was directed towards determining if the "high" exposure to AS_2O_3 (arsenic trioxide) of employees of the ASARCO Copper Smelter had adverse neurological responses as compared with their "low" exposed counterparts, the main categorical demographic classification was employer type. The ASARCO management furnished subjects with "high" exposure and "low" exposure as follows:

A. Men working in plant locations by way of job classification, where the arsenic exposure was "high".
B. Comparable men (age wise) where exposure was "low" by way of job classification.

Since the "high" exposure group was defined to be 200 μg/liter or more for at least the past five years, this automatically defines the "low" exposure group also. Some of our observations on available variables follow:

Demographic variables:

1. Four employer groups:

	*Number**	
ASARCO High exposure	37	(32)
ASARCO Low exposure	33	(28)
KAISER ⤳ Non ASARCO	13	(9)
TACOMA ⤳ Non ASARCO	28	(24)
Total number of volunteers	111	(93)

2. Age

The median ages in ASARCO High and Low are both around 51 years. The mean ages in ASARCO High and Low are both around 47 years. This is to be expected as the "volunteers" are matched by age!

In Kaiser Aluminum the median and mean ages are around 36 and 37 years respectively. Also, in Tacoma, the median and mean ages are around 37 (39) and 38 years respectively.

As aging is generally accepted to have an adverse effect on neurological responses, it is worth noting the statistical significance of the difference in the ages of the control (non-ASARCO) and ASARCO High or Low with $p = .001$ ($p = .011$). This indicates the necessary caution to be used in assigning the basis for the differences in the groups.

3. Smoking; Amount Smoked

The smokers and nonsmokers' distribution as well as the amount smoked by different employer types is significant with $p < .05$ ($p < .01$) and should be taken into consideration as related to neurological responses.

4. Urine Specific Gravity

The distribution of this variable is significantly different over the strata with unknown effect on the neurological response with $p = .0204$ ($p = .0237$).

5. Urine Creatinine Mg%

The distribution of this variable is significantly different over the strata with unknown effect on the neurological response with $p = .0072$ ($p = .0017$). Range (22 to 408)

6. Carboxyhemoglobin as of % of Hemoglobin

Carboxyhemoglobin as a percentage of hemoglobin is known to adversely affect the immunological balance and perhaps will affect the neurological response adversely. The distribution of this variable is found to be significantly different over the strata of employer type and high-low exposure group with $p = .009$, ($p = .007$). Smoking frequency is highly correlated with carboxyhemoglobin ($r = .73$).

Comment: The smoking, urine specific gravity, urine creatinine and carboxyhemoglobin all indicate the TACOMA group not to be comparable to the other groups.

Significant Response Variables

7. Ulnar Sensory Amplitude

The mean of this neurological response variable is significantly different over the employer types including the High-Low exposure groups in ASARCO, $p = .0007$ ($p = .0004$). There appears to be one

* Throughout the report numbers in parentheses indicate results omitting data for excuses, e.g., in the ASARCO group (total of 69) there were nine excuses, one case without ulnar sensory measures, two without arsenic in nails measures, three without arsenic in hair measures and one case without clinical findings. Therefore, the sample size will vary according to the analysis done.

outlier (#136) which, if eliminated, would contribute to an even higher level of significance.

8. Peroneal Amplitude Ankle

   The mean of this neurological response variable appears to vary, p = .06, over the high-low and other employer strata. When "excuses" are omitted the p value changes to .43. This is mostly due to the change made in the KAISER group.

9. Peroneal Amplitude Knee

   The mean of this neurological response variable is significantly different over the groups, p = .05. Removal of "excuses" with its resulting change for the KAISER group brings p to .38.

   Comment: The two ASARCO groups appear to differ from the KAISER and TACOMA groups. Since age correlates with each of the neurological measures at about −.30 it is difficult but necessary to separate the age effect and the group effect.

10. Urinary Arsenic

    Some measure of arsenic is used in forming the strata with the higher values corresponding to ASARCO High. Therefore, we can expect the groups to differ at a high level of significance.

    Given that they have significantly high arsenic levels in the ASARCO High group, we shall analyze the relationship of this variable to others measured in a later section.

Multivariate Analysis

The following are selected comments on multivariate procedures which should be helpful to the reader.

Factor analysis is a technique for discovering linear combinations of variables which "explain" the major factors or directions of variability in a group of individuals. The factors are estimated by least squares techniques and are uncorrelated with each other. Improvements in this and other multivariate analyses can be expected by using transformations that improve the linearity of the interrelationships of the variables and that equalize the variability of measurement error for different individuals.

Discriminant analysis is a technique for discovering linear combinations of the variables (similar to the factors above) which best "separate" the groups under study. The criterion is the ratio of the distance between the groups to the standard error of the discriminating factors. Again improvements in linearity or homogeneity of variances can improve the discrimination.

Canonical analysis is a technique designed to estimate the pairs of linear functions of variables (one from each of two groups) which are most highly correlated. We thus obtain indications of the factors in one group that are related to factors in the other group.

The tables discussed in this section of the report present the results of the multivariate approach with the corresponding interpretations, including appropriate transforms on the response variables, to supplement the various univariate analyses carried out in the preliminary statistical analysis.

A comparative factor analysis on the response variables between the raw and transformed (logs and reciprocals) measures was undertaken. A Log_{10} transformation on the amplitudes and an inverse transformation on the velocities and duration improved the separation of the factors. These transformations also increased the discrimination between the groups. Log transformations were taken on the arsenic level measures to reduce the skewness in their distribution.

The logarithmic transformation for amplitudes and for dose are fairly standard as is the reciprocal for velocities. The subsequent reporting is for the transformed variables.

Some observed associations on neurological responses vs. arsenic

1. Lower ulnar sensory amplitude and lower peroneal velocity are associated ($p \leq .01$) with higher arsenic levels in the urine, hair and nails.
2. Lower peroneal amplitude at ankle and knee are also associated with higher arsenic levels in the urine, hair, and nails. (The variables are appropriately transformed.) There are too few non-zero blood readings to expect definitive results using that variable.
3. *Discriminant Analysis of the Data:* The discriminant function separating the ASARCO group from the non-ASARCO group gives 69.1% correct classification for the ASARCO group and 67.5% correct classification for the non-ASARCO group respectively. The variables (original readings) that constituted the discriminant function were discovered to be the neurological response variable consisting of 1) logarithm of the ulnar sensory amplitude and 2) reciprocal of the peroneal motor conduction velocity ($p \leq .0005$). The percentages reported are for "jackknifed" analyses. This is a procedure to approximately adjust the percentage correct classification for the bias due to evaluating the results on the same observations used to determine the discriminating function.

   The discriminant analysis showed that the stepwise results of separating ASARCO from non-ASARCO employees is not improved by including more than the three measures—log ulnar sensory amplitude, log peroneal amplitude, knee, and inverse ulnar velocity, elbow to axilla. . . . The raw and transformed data indicated the significance of the same three measures, whether revised or original. Appendix Table 18 gives the jackknifed classification results after three steps.
4. *Factor Analysis of the Data:* For a breakdown of the employee groups, consisting of ASARCO High, Low, Non-ASARCO and all employees combined, a factor analysis placed neurological response variables among the first three factors as shown in Appendix Table 19. The first three factors explain between 50% and 60% of the total variance of the neurological variables.

   First of all, amplitudes, whether they are action potential amplitude or peroneal amplitudes at any

TABLE 18—Discriminant Analysis Jackknifed Classification Tables after Three Steps

Original Readings				Revised Readings			
a. Raw measures, priors = .63, .37							
Group	*% Correct*	*ASARCO*	*Controls*	*Group*	*% Correct*	*ASARCO*	*Controls*
ASARCO	85.3	58	10	ASARCO	88.4	61	8
CONTROLS	37.5	25	15	CONTROLS	26.8	30	11
TOTALS	67.6	83	25	TOTALS	65.5	91	19
b. Transformed measures, priors = .63, .37							
Group	*% Correct*	*ASARCO*	*Controls*	*Group*	*% Correct*	*ASARCO*	*Controls*
ASARCO	79.4	54	14	ASARCO	87.0	60	9
CONTROLS	22.5	31	9	CONTROLS	36.6	26	15
TOTALS	58.3	85	23	TOTALS	68.2	86	24
c. Transformed measures, priors = .50, .50							
Group	*% Correct*	*ASARCO*	*Controls*	*Group*	*% Correct*	*ASARCO*	*Controls*
ASARCO	69.1	47	21	ASARCO	56.5	39	30
CONTROLS	67.5	13	27	CONTROLS	65.9	14	27
TOTALS	68.5	60	48	TOTALS	60.0	53	57

joint in the body, seem to behave alike. In the same way velocities seem to behave alike except for the peroneal velocity. The factor analysis revealed that the neurological response variables that are "affected" in some way by playing a role in accounting for the factors are the amplitude variables and the only velocity variable was the peroneal.

The ulnar amplitudes at axilla, elbow and wrist appear together in Factor 1 whatever the group. The peroneal amplitudes (ankle and knee) appear in the second factor whatever the group. Factor 3 appears to be an assortment of velocities primarily. We do not see any distinguishing differences in these factors from one group to another.

5. *Test-Retest Study*

Let us now compare these factors with test-retest loadings of original vs. revised "blind" sub-sample of ten employees. We have used loadings (those greater than or equal to .70) and found the distributions of measures across the first three factors to be consistent with the ASARCO Low and High exposure groups from which they were drawn. The four sub-samples also compare well with each other, although the order of significance of the factors vary. See Appendix Table 20.

In addition to the factor analysis, we compared the average differences of the response measures taken not only between the test and retest, but also between the original and the revised data we later received. Appendix Table 21 shows that perhaps the computational errors were larger than the measurement errors.

TABLE 19—Rotated Factor Loadings (Patterns) > .50

A. For all employee groups combined, the distribution of response variables over the first three factors is:

Factor 1		*Factor 2*		*Factor 3*	
U. amp. elbow	(.976)	P. amp. ankle	(.976)	P. vel.	(.748)
U. amp. axilla	(.967)	P. amp. knee	(.973)	U. sensory vel.	(.673)
U. amp. wrist	(.969)			Sural vel.	(.692)

B. For ASARCO High the distribution of variables over the factors is:

Factor 1		*Factor 2*		*Factor 3*	
U. amp. elbow	(.968)	P. amp. ankle	(.889)	U. vel. wrist-elbow	(.728)
U. amp. axilla	(.965)	P. amp. knee	(.860)	Sural amp.	(−.617)
U. amp. wrist	(.929)				

C. For ASARCO Low the distribution of + variables over the factors is:

Factor 1		*Factor 2*		*Factor 3*	
U. amp. elbow	(.958)	P. amp. ankle	(.964)	P. vel.	(.735)
U. amp. axilla	(.956)	P. amp. knee	(.953)	Sural vel.	(.666)
U. amp. wrist	(.957)			U. sensory vel.	(.598)
				U. vel. wrist-elbow	(.542)

D. For Non-ASARCO the distribution of the variables over the significant factors is:

Factor 1		*Factor 2*		*Factor 3*	
U. amp. elbow	(.958)	P. amp. ankle	(.958)	P. vel.	(.865)
U. amp. axilla	(.961)	P. amp. knee	(.963)	U. sensory amp.	(−.615)
U. amp. wrist	(.969)	U. sensory vel.	(−.554)	Sural vel.	(.560)
		U. vel. duration	(.536)		

TABLE 20—Rotated Factor Loadings ≥ .70 on Test-Retest Samples (Original and Revised)

A. Original Test					
Factor 1		*Factor 2*		*Factor 3*	
P. amp. ankle	(.927)	U. amp. elbow	(.777)	U. vel. duration	(−.756)
P. amp. knee	(.966)	U. amp. axilla	(.843)	Sensory vel.	(.712)
U. vel. wrist-elbow	(−.792)	U. amp. wrist	(.822)		
B. Original Retest					
Factor 1		*Factor 2*		*Factor 3*	
U. amp. elbow	(.973)	Sural vel.	(.802)	P. amp. ankle	(.941)
U. amp. axilla	(.954)	U. vel. elbow-axilla	(.785)	P. amp. knee	(.920)
U. amp. wrist	(.954)	U. vel. duration	(−.775)		
C. Revised Test					
Factor 1		*Factor 2*		*Factor 3*	
U. amp. elbow	(.979)	P. amp. ankle	(.979)	P. vel.	(.885)
U. amp. axilla	(.984)	P. amp. knee	(.949)	Sural vel.	(.738)
U. amp. wrist	(.967)	U. vel. elbow-axilla	(−.843)	U. vel. wrist-elbow	(.736)
D. Revised Retest					
Factor 1		*Factor 2*		*Factor 3*	
U. amp. elbow	(.975)	P. amp. ankle	(.873)	U. vel. wrist-elbow	(.906)
U. amp. axilla	(.962)	P. amp. knee	(.930)	U. vel. elbow-axilla	(.733)
U. amp. axilla	(.962)	Sural amp	(.753)		
Sural vel.	(.831)				

In Table 22 we present the standard errors of the various neurological measurements as obtained originally and as revised. Also, we have analyzed the data in raw form as well as transformed. The important findings are in the final two columns of the table. The ratio for the raw data ranging from .53 up to 1.00 indicates the greater amount of information available from the revised data; e.g., a ratio of .71 noted for the peroneal amplitudes at ankle and knee indicates a factor of 2.0 improvement in precision $1/(.71)^2$. We can seek even further improvement by taking the transform; e.g., for peroneal amplitude knee the factor is $4.0 = 1/(.50)^2$. These factors are so large (and for some of the measurements even larger) that we could expect a much more definitive analysis using revised data for the whole study.

6. *Canonical Analysis of the Data:* While there is no demonstrable separation between the strata, namely the ASARCO High, ASARCO Low and non-ASARCO, the neurological responses most related to the combined arsenic levels in urine, hair and nails are:
   a. Peroneal Amplitude Ankle
   b. Peroneal Amplitude Knee
   c. Ulnar Sensory Amplitude, and
   d. Peroneal Motor Conduction Velocity.

TABLE 21—Ranks of Average Differences in Test-Retest Study. (Smallest Average Difference = Rank 1.)

Neurological Measures	A Original Test vs. Retest	B Revised Test vs. Retest	C Test: Original vs. Revised	C Retest: Original Revised
1. Ulnar Velocity, Wrist-Elbow	3	2	1	4
2. Ulnar Velocity, Elbow-Axilla	3	4	2	1
3. Ulnar Action Potential Duration	3.5	3.5	1.5	1.5
4. Ulnar Amplitude, Wrist	1	2	4	3
5. Ulnar Amplitude, Elbow	1	2	3	4
6. Ulnar Amplitude, Axilla	2	1	3	4
7. Ulnar Sensory Velocity	3	1	2	4
8. Ulnar Sensory Amplitude	2	4	1	3
9. Peroneal Motor Conduction Velocity	1	2	4	3
10. Peroneal Amplitude, Ankle	2	3	1	4
11. Peroneal Amplitude, Knee	2	3	1	4
12. Sural Velocity	4	3	1	2
13. Sural Amplitude	4	2	3	1
Average Rank	2.4	2.5	2.12	2.96

TABLE 22—Standard Error of Differences, Test-Retest Study.

Neurological Measures	Orig. test-retest		Revised test-retest		Ratio Rev/Orig	
	raw	transform	raw	transform	raw	transform
1. Ulnar Velocity, Wrist-Elbow	4.07	.00128	2.12	.00065	.52	.51
2. Ulnar Velocity, Elbow-Axilla	5.95	.00172	5.69	.00166	.96	.96
3. Ulnar Action Potential Duration	1.36	.01080	1.36	.01080	1.00	1.00
4. Ulnar Amplitude, Wrist	3.25	.230	2.89	.106	.89	.44
5. Ulnar Amplitude, Elbow	3.42	.264	1.80	.073	.53	.28
6. Ulnar Amplitude, Axilla	3.02	.236	1.89	.080	.63	.34
7. Ulnar Sensory Velocity	7.01	.00346	3.90	.00116	.56	.34
8. Ulnar Sensory Amplitude	4.16	.168	2.36	.111	.57	.66
9. Peroneal Motor Conduction Velocity	1.90	.00100	1.84	.00086	.97	.86
10. Peroneal Amplitude, Ankle	2.09	.179	1.48	.111	.71	.62
11. Peroneal Amplitude, Knee	1.84	.179	1.31	.090	.71	.50
12. Sural Velocity	2.25	.00149	2.03	.00125	.90	.84
13. Sural Amplitude	5.08	.200	5.09	.226	1.00	1.13

This finding is based on a canonical correlation analysis taking the individual values of the arsenic levels in blood, hair, nails and urine as one group and the revised or original neurological readings as the other group. We have significance $p = .007$ for the first factor (originally $p = .07$) using the revised electrical readings. See Appendix Table 23.

Using this analysis as an indication of the possibly important variables from the sum of the log levels of arsenic in urine, hair and nails and a "neurological" variable from the sum of the log amplitudes for ulnar sensory, peroneal ankle and peroneal knee reduced by the reciprocal velocity, peroneal. These are the variables "suggested" by the canonical analysis. We found these macro variables to be correlated at $-.467$ ($p \leq .0005$) for ASARCO employees. With "excuses" omitted the correlation is $-.430$ ($p \leq .005$). Non-ASARCO individuals were not included in this analysis.

The nine tables and the two remaining figures in the Appendix provide the data for the final sets of analysis devoted to dealing with the effects of "excuses", smoking and age. Thus, Table 24 not only includes the sets of correlation and regression coefficients but also lists the means, standard deviations and p-values for age, amount smoked, MNV (the macro-neurological variable) and MAL (the arsenic load macro-variable) for the four groups of employees. The four groups differ significantly on all four variables. We can see the need for the analysis in Table 25 since the controls are younger and the KAISER group smokes less. We can also note the difficulty in showing a difference between the high and low exposure groups at ASARCO since both have a high arsenic load and the "excuses" show similar results. Table 26 shows the correlations of age, amount smoked and arsenic load with the macro-neurological variable for the four employee groups. Table 27 repeats some of the correlations of Table 26 and includes also some additional partial correlations which may clarify the fact that the relationships to age and smoking do not appreciably affect the relationship of arsenic to neurological response. There is no evidence that including the "excuses" would vitiate these findings when they are included in the analysis. Table 28 shows how comparable they are with respect to the macro-neurological variable generated. Table 29 shows a similar result for those above maximum arsenic load. Table 30 reports the comparison for those who were below normal-neurologically and above normal maximum arsenic load. The relationship between the neurological measure and arsenic is significant as shown by the chi-square analysis of Table 31. The relationship between the neurological measure and arsenic remains significant even when persons with excuses are removed. (See Table 32).

Appendix Figure 6 presents a chart showing the reduced neurological response related to increasing arsenic load of the groups under study. Appendix Figure 7 is a similar presentation but is based on the data for individual employees. There is no reduction in neurological response for the controls, a lower response level for the ASARCO low exposure group and *dose-dependent* further response with increasing arsenic load for the high exposure group and for the "excuses" group. The "excuses" group's neurological response is also arsenic "dose" dependent at a smaller dose level than the non-excuses group. As seen in Appendix Figure 7, the "excuses" slope parallels the high exposure non-excuses slope but is shifted back to a lower arsenic load, i.e. neurological loss is dose dependent and greater in amount of loss.

TABLE 23—Canonical Variable Loadings. Restricted to Variables with Loadings. > .40 in any canonical variable.

		FIRST CANONICAL VARIABLE	
		Original Data	Revised Data
Group 1:	arsenic blood	.331	.160
	arsenic urine	.802	.815
	arsenic hair	.855	.893
	arsenic nails	.864	.688
Group 2:	ulnar sensory amp.	−.771	−.685
	peroneal amp. ankle	−.555	−.585
	peroneal amp. knee	−.539	−.602
	peroneal vel.	.410	.647

TABLE 24—Correlation Results of Neurological Macro Variable against Arsenic Macro Variable, adjusting for age and smoking.

PEARSON CORRELATIONS	EXCUSES REMOVED ASARCO (n = 54)	EXCUSES REMOVED CONTROLS (n = 33)	EXCUSES REMOVED ALL (n = 87)	EXCUSES ALL (n = 16)	EXCUSES ASARCO (n = 9)	ALL ASARCO (n = 64)	ALL EMPLOYEES (n = 103)
1. AGE vs. NEUROS	.0329	−.4079 (p ~ .02)	−.1934 (p ~ .03)	−.4935 (p ~ .03)	−.5043	−.0376	−.2559 (p ~ .005)
2. AMT. SMOKED vs. NEUROS	−.1873	−.1946	−.2274 (p ~ .02)	−.3558	−.2152	−.1837	−.2477 (p ~ .007)
3. AGE vs. ARSENIC LOAD	.0991	−.2097	.3035 (p ~ .002)	.5150 (p ~ .025)	.1929	.0757	−.3475 (p ~ .005)
4. AMT. SMOKED vs. ARSENIC	.0906	−.0062	.1724	.1529	.0607	.0988	.1964 (p ~ .025)
5. NEUROS vs. ARSENIC LOAD	−.2802 (p ~ .025)	.0578	−.3695 (p ~ .001)	−.7285 (p ~ .001)	−.6918 (p ~ .020)	−.430 (p ~ .005)	−.4443 (p ~ .0001)
PARTIAL CORRELATIONS							
6. NEUROS vs. ARSENIC (age & amt. smoked partialed out)	−.2672 (p ~ .05)	−.0302	−.2916 (p ~ .005)	−.6050 (p ~ .01)	−.7533 (p ~ .01)	−.3234 (p ~ .008)	−.3444 (p ~ .005)
MULTIPLE CORRELATIONS							
7. NEUROS vs. ARSENIC, AGE AND AMOUNT SMOKED	.3240 (p ~ .02)	.4422 (p ~ .01)	.4224 (p ~ .001)	.7962 (p ~ .001)	8884 (p ~ .002)	.3327 (p ~ .005)	.4947 (p ~ .0001)
REGRESSION COEFFICIENTS							
	INTERCEPT	2.493	3.196	2.756	3.724	8.559	2.799	2.892	F's
	AGE	.004	−.403	−.128	−.247	−.618	−.075	−.156	(2.89)
Standardized	AMT.SMOKED	−.162	−.169	−.192	−.303	−.470	−.178	−.196	(5.01)
	ARSENIC LOAD	−.266	−.028	−.298	−.555	−.544	−.319	−.351	(14.27)

We may sum up our findings by stating that the macro-neurological variable (MNV) is related to age in general, but is not correlated to age in the ASARCO employees. This is also true for the macro-variable for arsenic load (MAL). The amount smoked is related to MNV in general and should probably be adjusted for in the analysis. The relationship is similar whether or not the employee was labeled "excuse". However, the

TABLE 25—Means and (Standard Deviations) and p-values.

INCLUDING "EXCUSES"	AGE	AMT. SMOKED (Log Scale)	NEURO.S (Macro Variable)	ARSENIC LOAD (Macro Variable)
High exposures, ASARCO n = 37	47.3(9.7)	.302(.267)	1.965(.697)	4.531(1.036)
Low exposures, ASARCO n = 33	46.6(11.6)	.314(.282)	2.113(.578)	2.186(.769)
TACOMA n = 13	37.8(11.9)	.342(.258)	2.451(.528)	.330(.325)
KAISER n = 28	38.8(9.4)	.133(.236)	2.399(.425)	.395(.481)
ALL GROUPS n = 111	43.9(11.1) p = .0012	.267(.272) p = .0220	2.177(.606) p = .0092	2.237(1.907) p = .0000
EXCLUDING "EXCUSES"				
High exposures, ASARCO n = 32	46.8(10.2)	.296(.265)	2.004(.656)	4.609(.975)
Low exposures, ASARCO n = 28	45.4(12.0)	.331(.281)	2.138(.541)	2.236(.753)
TACOMA n = 9	38.0(11.6)	.441(.206)	2.361(.584)	.305(.366)
KAISER n = 24	38.4(9.5)	.135(.241)	2.382(.448)	.383(.473)
ALL GROUPS n = 93	43.3(11.3) p = .0114	.296(.265) p = .0093	2.178(.578) p = .0741	2.315(1.935) p = .0000

TABLE 26—Correlations with Macro-Neurological Variable.

	ASARCO HIGH	ASARCO LOW	KAISER	TACOMA	ALL
INCLUDING "EXCUSES"					
AGE	−.259 (n = 36)	.134 (n = 33)	−.445 (n = 13)	−.282 (n = 28)	−.246 (n = 110)
AMT. SMOKED	−.191 (n = 36)	−.160 (n = 33)	−.670 (n = 13)	−.085 (n = 28)	−.242 (n = 110)
ARSENIC LOAD	−.557 (n = 33)	−.105 (n = 31)	.598 (n = 13)	−.069 (n = 28)	−.430 (n = 105)
EXCLUDING "EXCUSES"					
AGE	−.182 (n = 31)	.202 (n = 28)	−.542 (n = 9)	−.335 (n = 24)	−.197 (n = 92)
AMT. SMOKED	−.226 (n = 31)	−.133 (n = 28)	−.704 (n = 9)	−.031 (n = 24)	−.215 (n = 92)
ARSENIC LOAD	−.489 (n = 28)	.028 (n = 26)	.623 (n = 9)	−.140 (n = 24)	−.370 (n = 87)

amount smoked is poorly related, if at all, to arsenic load. The macro variables for arsenic load and neurological response are not related in the controls, but are related in the ASARCO employees (even more strongly in the "excuse" group). There is evidence that all three factors, age, smoking and arsenic reduce neurological function when taken together. All groups show a significant overall effect from these three factors. If we remove by regression the effect of smoking and age on neurological response, we find very little reduction in the correlation of MNV and MAL. We can state that the relation of the neurological variable to arsenic load is not an artifact of age or amount of smoking among ASARCO employees. The control group continues to show a significant overall effect from these three factors.

The conclusion of the analysis is that there is a statistically significant relationship between arsenic load and reduced neurological response in the smelter population.

Discussion

There are a number of points that seem to merit comment. First, the subjects were volunteers from a selected set of ASARCO employees or volunteer participants following a general appeal and therefore it is hard to assess the representativeness of the samples from their respective strata. Then, the levels of arsenic measured in the urine of the ASARCO high men are substantially lower than those furnished by the company from records dating back, in some instances, many years. There is also some evidence in the historical data of a trend to lower average values with the passage of time, but the data are scanty. Whether this phenomenon is real or is a product of collection, handling, and laboratory procedure differences with the urines cannot be determined from the data at hand. Nevertheless, the ASARCO High group is clearly distinguishable from the ASARCO Low in urinary arsenic values as well as arsenic in hair and nails. The levels of lead in the participants as a total group also appear to be lower than that found in other studies. No reason for the lower values has been determined by the laboratory making the determinations. Also, the electrophysical examination produces values for the various velocities and amplitudes used in this analysis that have relatively large components of variation due to day-to-day variability within the same individual and to measurements made on the tracing from the test equipment. Recalculating the electrical parameters late in the study

TABLE 27—Correlations and Partial Correlations Associated with Age and Smoking.

	EXCUSES REMOVED ASARCO (n = 54)	EXCUSES REMOVED CONTROLS (n = 33)	EXCUSES REMOVED ALL (n = 87)	EXCUSES ALL (n = 16)	EXCUSES ASARCO (n = 9)	ALL ASARCO (n = 64)
Neuro vs. Arsenic	−.280	.058	−.370	−.727	−.692	−.430
adj. (age)	−.285	−.031	−.332	−.636	−.702	−.341
adj. (smoke)	−.269	−.021	−.344	−.730	−.696	−.332
adj. (age + smoke)	−.207	−.030	−.293	−.605	−.753	−.323
Neuro vs. Smoke	.091	−.006	.172	.153	.061	.099
adj. (age)	−.187	−.185	−.259	−.486	−.589	−.209
Neuro vs. Age	.033	−.408	−.193	−.494	−.504	−.038
adj. (smoke)	−.034	−.374	−.231	−.582	−.699	−.110

TABLE 28—Number Below Normal Minimum Neuro-Clinical Finding

	No	Sen	Motor	Both	Total
ASARCO high	2	3	1	2	8
low	2	1	1	0	4
Controls	2	0	0	0	2
Excuses	1	2	0	1	4
Total	7	6	2	3	18

TABLE 30—Number Below Normal Minimum Neuro and Above Normal Maximum Arsenic Load-Clinical Finding

	No	Sen	Motor	Both	Total
ASARCO high	2	3	1	2	8
ASARCO low	0	0	1	0	1
Controls	1	0	0	0	0
Excuses	1	1	0	1	3
Total	3	4	2	3	12

and subsequent analysis of these new values appears not to markedly change any earlier findings. The presence of these variations only adds to the difficulty of detecting other factors that may be associated with the electrical variables. This may be the reason that no significant regression of amplitudes or velocities on any of the metal-tissue combinations taken singly could be found. In many of the scatter plots there was a suggestion of a decrement in nerve function with increasing levels of the metals in the tissues, but the "noise" in the system made detecting the decrement by statistical procedures extremely difficult. Transformations and the development of an index of neurological status demonstrated an association of arsenic in urine, hair and nails with neurological deficits. The association of the macrovariables from the multivariate analysis further strengthened this finding.

The multivariate analysis did show that some of the neurological responses are associated with the arsenic levels in the tissues of the subjects. Indications of this relationship were present in the original data and were strengthened when the revised neurological readings were used. This should add confidence to the findings of this study. The establishment of a dose-response relationship is a first and necessary step in studying the possibly harmful effects of heavy doses.

The issue of the biological importance of the association between arsenic levels and neurological deficit is difficult to assess. While the clinical neuropathies diagnosed were all mild, non-disabling, and generally not recognized by the men with these diagnoses, any loss of function that could be avoided by preventive measures cannot be regarded as unimportant or trivial.

What is a neuropathy? A peripheral neuropathy is any disorder that affects the peripheral nerves and interferes with their normal functioning. We know the peripheral nerves are those parts of the nervous system that carry the messages from the spinal cord to the muscles or the sensory messages from the skin to the central nervous system, namely the spinal cord, and then ultimately the brain. Clinically, the peripheral nerve can be affected by many processes, some metabolic as in diabetes, others that are toxic as can be seen in association with alcoholism or with heavy metals such as arsenic or lead. Arsenic is known to cause a sensory motor neuropathy. In the chronic low grade form of arsenical intoxication, it is more likely that a sensory neuropathy will occur with relatively minor motor signs, namely weakness. In acute intoxications however, there is both loss of sensation and profound weakness.

There is clinical and histologic evidence of changes in nerves of some individuals who have been exposed to arsenic. In an industrial environment, the mode of intoxication may possibly be predominately from ingestion of airborne particles, a finding which has long been recognized as leading to a neuropathic picture. Petren points out that with ingestion as major mode of entry, a polyneuropathy can be expected.[35] This may be the major type of exposure and route of entrance into the body in the workers in a smelter. The requirement of face masks by the smelter in certain job categories may have diminished the exposure of these workers.

As indicated above, a significant number of individuals have both clinical as well as sub-clinical signs of neuropathy. By sub-clinical neuropathy is meant an individual who, on neurologic examination states that he has no subjective complaints of numbness or pins and needles feelings in his fingers and there is no evidence of decreased appreciation of sensation to pin touch, temperature, position or vibration sense in the fingers or hands. There is no weakness and there is no reflex loss. These individuals, however, will show on nerve conduction studies a slowing of conduction velocity both in motor and in sensory nerves. (See attached ranges of normal values.) These values represent, for example, that the ulnar sensory was 50-70 meters per sec. and the action potential amplitude was 8-28 microvolts. By recording the evoked response on film from the muscle belly after stimulating the appropriate nerve, one measures not only

TABLE 29—Number Above Normal Maximum Arsenic Load

	No	Sen	Motor	Both	Total
(n = 29) ASARCO high	12	8	2	3	25
(n = 26) ASARCO low	3	3	1	0	7
(n = 34) Controls	0	0	0	0	0
(n = 16) Excuses	1	1	0	1	3
Total	16	12	3	4	35

TABLE 31—All Cases

		NEURO ≥1.55	NEURO <1.55		
ARSENIC	>3.05	23	12	35	$x^2 = 10.86$
	≤3.05	64	6	70	$p < .005$
		87	18	105	

TABLE 32—ASARCO Cases Without Excuses

		NEURO ≥1.55	NEURO ≤1.55		
ARSENIC	>3.05	23	9	32	$x^2 = 6.53$
	≤3.05	0₂ 23	3₁ 12	3 35	$p < .01$

how long it takes for that electrical signal to appear after stimulating the appropriate nerve but also one assesses the voltage and the wave form. These measures indicate whether or not there is any abnormality.

Since this technique has become available, ranges of normal have been established for men and women and have to some extent been correlated with age. There is a suggestion that there is some slowing of conduction velocity with age though the effect of age does not seem to be very marked.

Those individuals who have a clinical neuropathy show both subjective and objective signs of decreased sensation, usually in a stocking and glove distribution, as well as having evidence of slowing of conduction by measuring the ulnar sensory conduction velocity, the motor conduction velocity of the ulnar nerve and the motor conduction velocity of the common peroneal nerve as well as the sensory conduction velocity of the sural nerve. This latter nerve supplies the lateral aspect of the

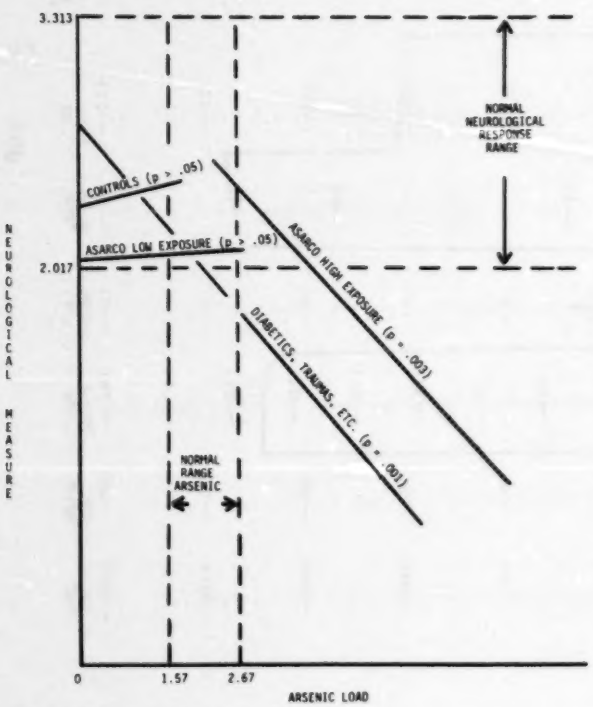


FIGURE 6. Regression Lines by Groups.

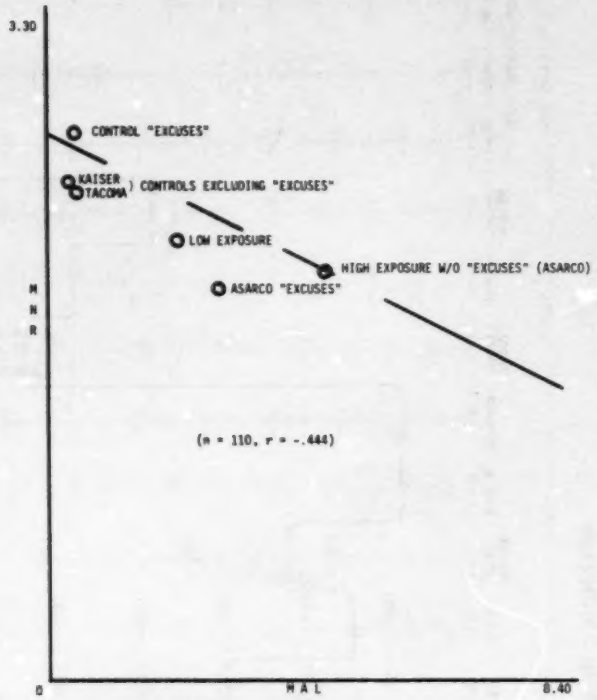
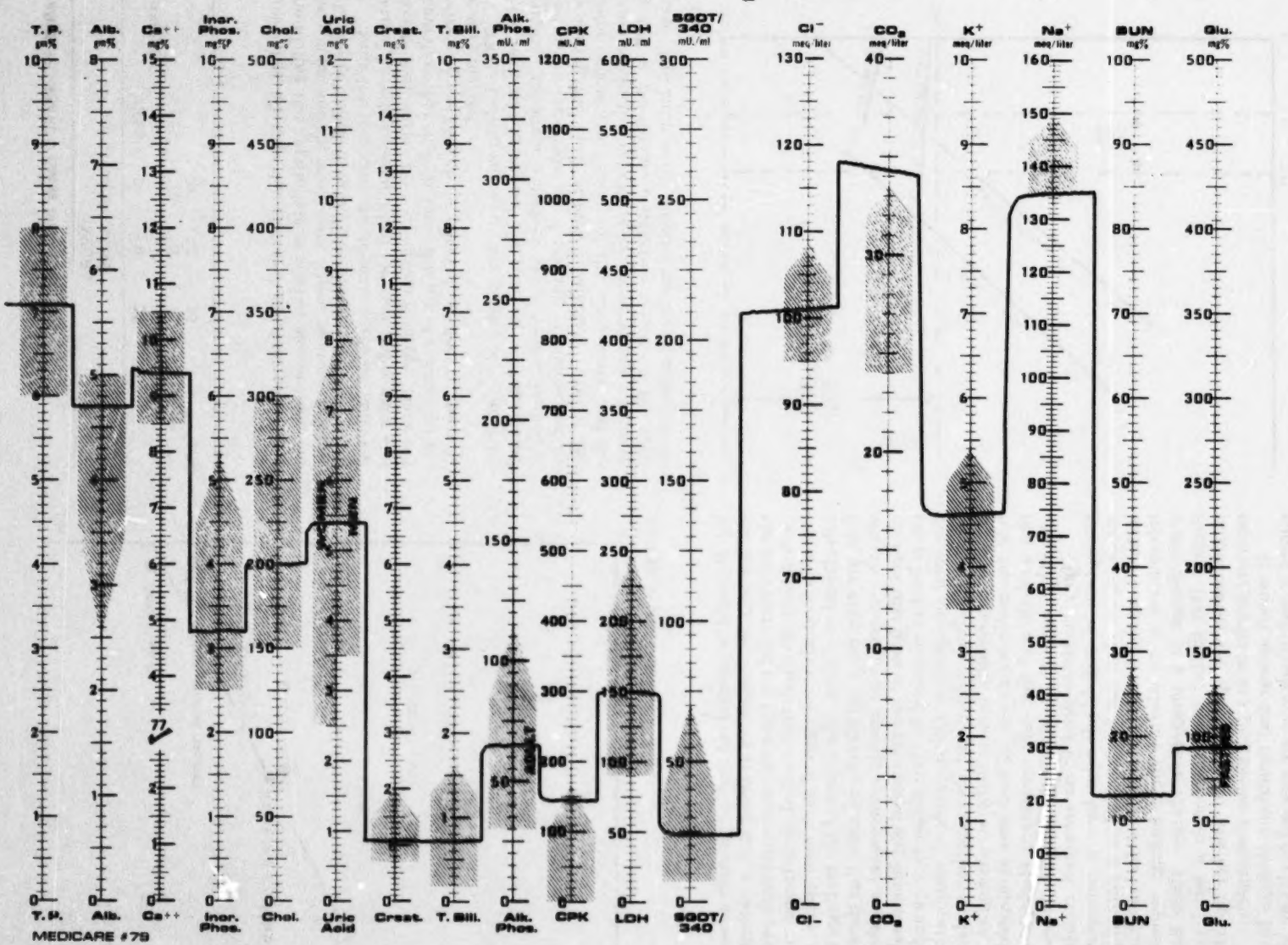


FIGURE 7. Macro Means

leg. It should be pointed out that in this study all workers did not consider themselves as being sick or patients and the examiners did not know the source of employment of each of the individuals they studied. Nonetheless, a number of individuals show signs of early neuropathy, either sub-clinical or clinical. The report of the findings, therefore, are even more significant and show that these individuals exposed to an arsenic environment are showing changes that have as yet not caused any functional deficit, at least as measured by their ability to work and carry out their occupations. Other causes of neuropathy i.e. those individuals who might have another explanation for their neuropathy such as diabetes, alcoholism, frostbite, traumatic events, etc. all have been eliminated from this analysis and the only recognized etiologic factor other than age and smoking is the exposure to arsenic.

Many questions need to be answered, clearly, the percentage of individuals who have a neuropathy is much higher than can be expected in a normal population. Since this is only one study, one does not have the information as to whether these findings represent a static change or a progressive change. These findings suggest that further investigations in a serial manner might answer the question as to whether the chronic exposure results in any progressive abnormality.

It would appear that neurologic changes have occurred in individuals who are exposed to chronic arsenic loads though the exact long-range significance of such an arsenic burden cannot be determined at this point. Cer-



APPENDIX C. Blood Graph Results

tainly, the clinical neurologic examination and the nerve conduction velocity studies, both of sensory and motor nerves, are sensitive means of defining an early change and are of such a nature that they are reproducible enough to be able to follow these changes in a sequential and serial manner.

The implications of this study are: That chronic arsenic exposure in an industrial setting affects the peripheral nervous system and the neurologic parameters involving both clinical and quantitative measurements are sensitive means of screening the population for changes related to arsenical neuropathies.

Summary

A pilot study in a copper smelter was undertaken to determine whether nerve conduction velocity can be utilized as a biological indicator of the subtle health effects of long-term exposure to airborne arsenic trioxide among a sample of residents of Pierce and King Counties, Washington. The study involved comparing active working men heavily exposed to arsenic in the work place with workers not so exposed.

Since in clinical practice arsenic is recognized as causing a peripheral neuropathy, this study was carried out to determine whether sustained industrial exposure to inorganic arsenic was associated with changes in neurologic response. This has not previously been looked for in workers with sufficient unimpaired ability to perform their required assignments.

The study team designed a double-blind electrophysiologic and clinical study of the experience of four groups of workers—two with varying levels of exposure to arsenic and two sets of controls. Demographic and other characteristics, including smoking, were obtained through use of a pre-tested questionnaire. The parameters studied included clinical examination (history and neurologic examination) and electrophysiologic tests of the sensory and motor nerve conduction in the upper and lower limbs. Levels of arsenic and eight other metals were measured in the blood, hair, urine and nail specimens collected. The study team screened the workers' blood for carboxyhemoglobin levels, diabetes mellitus and anemia. The neurological status of the men was categorized both on the clinical judgement of the examining neurologist and the objective measurements from the electrophysiocologic examination. Care was taken in the analysis not to confuse age effects with other effects.

To reduce the dimensionality of the neurological measurements, a classification of clinical neuropathy, sub-clinical neuropathy, and normal was developed. Men classified as cases of subclinical neuropathy had to exhibit either one or more reduced velocities, or two or more nerves with reduced amplitudes. The classification clinical neuropathy was based on the neurologist's diagnosis. All other men were classified as normal.

With this classification into clinical neuropathy, subclinical neuropathy, and normal categories, a statistically significant association was demonstrated with the sum of the logarithms of arsenic levels in urine, hair and nails. This association remained after adjustment for smoking, "excuses" and average age differences in the categories of the new classification.

Accordingly, there is unequivocal evidence that a statistically significant relationship exists between arsenic exposure and reduced neurological function in this industrial population.

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APPENDIX A. Questionnaire

Application No. 6-289-A, "Association of Nerve Conduction Times and Exposure to Arsenic in ASARCO Employees".

1. Participant number _____
2. Last Name _____ _____ 01
3. First Name _____
4. Middle Initial _____
5. Street Address _____
6. City _____
7. State _____
8. Zip _____
9. Name of your Physician _____
10. Address of your Physician _____
11. Birthdate _____ _____
12. Date test administered _____ _____
13. Have you lived at the above address for more than 1 year?

    Yes _____ (0) No _____ (1)
14. If no, what was your previous address?

    _____

    street city state zip
15. How long did you live at the previous address? _____
16. How long ago did you take your urine sample? _____ _____
17. Have you eaten shellfish in the past 36 hours? Yes _____ (0) No _____ (1)
18. Have you had any recent injuries or operations? Yes _____ (0) No _____ (1)

19. If yes, describe _____

_____

20. Have you ever taken any of the following types of medicines?

a. Anti-convulsants (anti-seizure medicines) (Dilantin, Phenurone, Tridione) — Yes _____ 0 No _____ 1 Don't Know _____ 9

b. Anti-tuberculous drugs (INH, PAS, pyrazinamide, ethionamide) — Yes _____ 0 No _____ 1 Don't Know _____ 9

c. Pills for diabetes (Diabinese, Orinase, Cymelor, Tolinase) — Yes _____ 0 No _____ 1 Don't Know _____ 9

d. Blood pressure medicines or water pills (Aldomet, Diuril, Hydrodiuril) — Yes _____ 0 No _____ 1 Don't Know _____ 9

e. Male hormones (methyltestosterone, oxymetholone) — Yes _____ 0 No _____ 1 Don't Know _____ 9

f. Thyroid drugs (Tapazole, propylthiouracil) — Yes _____ 0 No _____ 1 Don't Know _____ 9

g. Antidepressants or major tranquilizers (not including barbituates, valium, librium, etc.) (Thorazine, Sparine, Mellaril, Stelazine, Compazine, Niamid, Nardil, Marplan, Parnate; Tofranil, Elavil) — Yes _____ 0 No _____ 1 Don't Know _____ 9

21. Have you ever taken other medications (not covered in the preceding list) for longer than 2 weeks at a time. Yes _____ 0 No _____ 1

22. If yes, list below

Name of drug	year prescribed	length of time drug taken	associated medical problems	

23. Have you ever taken medicines containing arsenic? Yes _____ 0 No _____ 1 Don't Know _____ 9

24. Have you ever had a substantial weight loss (more than 10 lbs) in the last three months? Yes _____ 0 No _____ 1 Don't Know _____ 9

25. If yes, what is the reason? Special diet _____ 1 Don't Know _____ 9

26. Do you have any history of liver disease? Yes _____ 0 No _____ 1 Don't Know _____ 9

27. Do you drink alcoholic beverages now? Yes _____ 0 No _____ 1

28. If yes, have you consumed any alcohol in the past 48 hours? Yes _____ 0 No _____ 1

29. If yes, what and how much?

_____

30. Do you currently smoke cigarettes? Yes _____ (0) No _____ (1)

31. If yes, how many per day?

less than ½ pack _____	_____ 1
½ to 1 pack _____	_____ 2
1 to 2 packs _____	_____ 3
over 2 packs _____	_____ 4

32. Do you get your drinking water from a well? Yes _____ (0) No _____ (1) Don't Know _____ (9)

33. Are you personally applying insecticides in your garden? Yes _____ (0) No _____ (1) Don't Know _____ (9)

APPENDIX B. Clinical Work Sheet

In: _____
No: _____

Name _____ Age _____ Sex _____

Date: _____ D.O.B: _____

_____ Duration in present position: _____

Other Factors:	Yes	No	Duration
Trauma			
Metabolic Disturbances			
Nutritional Disburbances			
Alcohol Consumption			
Medication:			

Neurological Signs:	RUE	LUE	LUE	ELE
Numbness				
Painful/Burning				
Pinprick				
Vibration Sense				
Muscle Weakness				

Reflexes	Bl	TR	Sup.	K	A	P
Left						
Right						

Room Temp: _____
Skin Temp: _____

APPENDIX C. Nerve Conduction Velocity Testing

In: _____
No: _____

NERVE: ULNAR R.

DISTAL LATENCY		(_____cm)	: _____
M.C.V. Ab. Elb - Wr.	(_____cm)	: _____	: _____

MOTOR	M.A.P. Ax - Ab. Elb.	(_____cm)	: _____	: _____
	Amplitude (neg-phase)			: _____
	Stimulation	_____		: _____
	Stimulation	_____		: _____
	Decrement	_____		: _____
SENSORY ACTION POTENTIAL	Amplitude		(_____)	: _____
	Form			
	Latency to Peak	_____	(_____cm)	: _____
	Latency to Onset	_____	(_____cm)	: _____
	Velocity to Onset	_____		: _____
NERVE: COMMON PERONEAL R.				
MOTOR	DISTAL LATENCY		(_____cm)	: _____
	M.C.V.		(_____cm)	: _____
	M.A.P.			
	Amplitude (neg-phase)			
	Stimulation	_____		: _____
	Stimulation	_____		: _____
	Decrement	_____		: _____
NERVE: SURAL	AMPLITUDE		(_____)	: _____
				: _____
	Form			: _____
SENSORY ACTION POTENTIAL	Latency to Peak	_____		: _____
	Latency to Onset	_____	(_____cm)	: _____
	Velocity to Onset	_____	(_____cm)	: _____

APPENDIX D. Coefficient of Each Metal

Coefficient of variation among blind and replicated samples for each metal: specimen set of data

		BLOOD	*URINE*	*NAILS*	*HAIR*
Pb	Blind	65.8%	68.4%	42.3%	76.2%
	Replicate	11.0%	8.6%	5.9%	5.5%
Hg	Blind	None	13.8%	68.1%	53.8%
	Replicate		5.4%	None	None
As	Blind	None	2.3%	40.7%	40.8%
	Replicate		None	8.6%	7.0%
Zn	Blind	39.2%	10.7%	15.5%	25.8%
	Replicate	None	None	3.1%	5.0%
Cu	Blind	11.9%	53.6%	34.4%	35.5%
	Replicate	14.8%	6.1%	6.3%	7.0%
Ni	Blind	18.1%	None	48.7%	78.1%
	Replicate	17.4%	16.7%	15.9%	15.0%
Cd	Blind	69.2%	75.6%	62.3%	60.5%
	Replicate	21.1%	12.2%	11.1%	8.6%
Sb	Blind	None	0	34.0%	69.2%
	Replicate		None	9.4%	6.6%
Se	Blind	4.0%	1.6%	49.8%	62.8%
	Replicate	None	32.2%	12.3%	18.9%

APPENDIX E. Cations in Biological Specimens

Normal levels and mean levels of cations found in biological specimens

		BLOOD ppb	URINE ppb	HAIR ppm	NAILS ppm
Normal	Pb	(100–350)	(10–35)	(0.5–360)	5–6
Found		144 ± 126	13.9 ± 13.4	123 ± 251	7.9 ± 11.7
Normal	As	(10–640)	(15–60)	(.045–1.7)	(.080–5.5)
Found		1.5 ± 8.9	38.2 ± 73.3	60.0 ± 122.3	29.3 ± 63.3
Normal	Cd	(.002–.007)	(1.4–30)	(0.20–1.0)	0.1 ± 10
Found		—	2.09 ± 2.97	1.07 ± 1.92	0.32 ± 0.80
Normal	Zn	(900–9000)	(630)	(150–200)	(180–220)
Found		8480 ± 2550	627 ± 385	215.7 ± 136.4	100.4 ± 40.4
Normal	Cu	(1230)	(10–50)	(2–20)	(45–60)
Found		968 ± 307	80 ± 284	58.8 ± 116.4	17.2 ± 33.7
Normal	Hg	(75–90)	(2–20)	(3–40)	1.0
Found		—	2.06 ± 3.48	—	—
Normal	Ni	—	—	.0	0.5
Found		—	—	13.1 ± 48.6	9.4 ± 51.1
Normal	Sb	—	—	(7.9–9.7)	2.0
Found		—	—	5.5 ± 11.4	0.78 ± 1.79

APPENDIX F. Assay of Biological Specimens

Sample and digestate size, normal values, analytical method and detection limits pertaining to biological specimens assayed during **the Tacoma Study.**

Sample Size / Analytical Volume	2–4 ml / 50 ml BLOOD	10 ml / 10 ml URINE	50–100 mg / 10 ml HAIR	50–100 mg / 20 ml NAILS	Normal Levels, Misc. Media	
normal levels (ppb)	100–500	15–60	45–1700	80–5600	Soil	500–14,000
ARSENIC	Arsine Generator	Arsine Generator	Furnace	Furnace	Hair	18,000–30,000
detection limit (ppb)	3–5	5–10	2–3	1–2.5		
MERCURY	75–90	2–20	3,000–40,000		Feces	10 μg/day
	Cold Vapor	Cold Vapor	Cold Vapor	Cold Vapor	Urine	0.5 μg/day
	0.1–0.3	0.1–0.3	0.1–0.3	0.1–0.3	Air	20 ng/m³
NICKEL	1.0–4.2	11	1000–4000		Blood	110
	APDC/Furnace	APDC/Furnace	Furnace	Furnace		
	2.3	10–15	2.5–5	2.5		
COPPER	1230	10–50	2,000–20,000	45,000–60,000	Plants	5,000–20,000
	C_2H_2 Flame	C_2H_2 Flame	C_2H_2 Flame	C_2H_2 Flame	Soil	30,000
	10–20	10–20	20–50	30–50	Urine	20–60 μg/day
ANTIMONY	APDC/Furnace	APDC/Furnace	7900–9700		Air	2 ng/m³
	1–2	2–5	Furnace	Furnace		
			0.5–1	0.5–1		
SELENIUM	200	10–150	300–6000	1,140	Air	3 ng/m³
	APDC/Furnace	APDC/Furnace	Furnace	Furnace		
			10–20	20–50		
CADMIUM	.002–.007	1.4–30	200–1000		Exposed Urine	600
	APDC/Furnace	APDC/Furnace	Furnace	Furnace	Milk	17–30
	.01–.03	.01–.03	.03–.05	.02–.05	Soil	60
					Plants	500

ZINC	900–9000 C_2H_2 Flame 30–50	630 C_2H_2 Flame 50–100	150,000–200,000 C_2H_2 Flame 20–30	180,000–220,000 C_2H_2 Flame 20–30	Serum Liver Bone Air Prostate Retina Intake	800–1600 60,000 60,000 0.1 μg/m³ 860,000 500,000 12 mg/day
LEAD	100–350 APDC/Furnace or Furnace 0.5–1	10–35 APDC/Furnace 1–3	500–360,000 Furnace 0.5–1	Furnace 30–50	Soil Plants Air Gas Intake	12,000 100,000 4μg/m³ 3.8g/imp. gal 300 μg/day

APPENDIX G. CLINICAL RESULTS

Suppressed to avoid identifying individual participants.

Case #	Results
	1
	1
	3
	1
	0
	0
	0
	4
	1
	0
	0
	1 (diabetic)
	1 (alcohol)
	2
	2
	0
	0
	0
	—
	1
	1
	0
	0
	0
	1 (frostbite)
	0
	0
	4
	0
	0
	1
	0
	0
	0
	0 (alcohol)
	—
	0 (alcohol)
	0
	1
	0
	—
	0
	0 (diabetic)
	—
	0
	0
	0
	0
	—
	0

Suppressed to avoid identifying individual participants.

Case #	Results
	0
	1 (alcohol)
	0
	0
	0
	—
	0
	0
	—
	0
	0
	0
	0
	3 (alcohol)
	4
	0
	1
	0
	0
	—
	4
	1
	0
	3
	1
	1
	0
	0
	0
	0
	4
	0
	0
	1
	0
	1
	1
	1 (diabetic)
	3
	1
	—
	0
	4
	0
	1
	4
	0
	1 (alcohol)
	0
	1 (alcohol)
	3

Suppressed to avoid identifying individual participants.

Case #	Results
	0
	1
	1
	4
	4
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	3
	—
	1
	0
	0
	0
	0
	0
	0 (alcohol)
	1
	4
	0
	0
	1 (alcohol)
	1
	1 (alcohol)
	2
	0 (spondylosis)

CODES

0 = NO NEUROPATHY
1 = SENSORY NEUROPATHY
2 = MOTOR NEUROPATHY
3 = SENSORY-MOTOR NEUROPATHY
4 = RETEST

APPENDIX H. Electrical Values

MOTOR ULNAR MCV Vel W-E	MCV Vel E-A	MAP Dura	AMPL. W	AMPL. E	AMPL. A	SENSORY VEL.	SENSORY AMPL.	MOTOR PERONEAL VEL.	AMPL. Ankle	AMPL. Knee	SENSORY SURAL VEL.	SENSORY SURAL AMP.
55 m/s	60 m/s	13.2	10.5	9.5	9.2	30.5 m/s	8 u	46.8 m/s	1.5	2	41 m/s	15 u
50 m/s	66 m/s	17.5 m/s	10	9.3	8.3	43 m/s	4.5 u	44 m/s	2.5	2.9	40 m/s	13 u
62 m/s	62 m/s	12.7	5	3.4	4	55 m/s	11 u	50 m/s	3	3	48 m/s	18 u
49 m/s	55 m/s	16.7	11.5	11	10.5	50 m/s	13 u	42 m/s	4	3.2	36 m/s	21.5 u
50 m/s	72 m/s	14	8.5	8.5	8.5	54 m/s	12 u	39 m/s	7.4	6.6	41 m/s	24 u
46 m/s	59 m/s	11.5	11	9	8.5	46 m/s	6 u	43 m/s	7.7	6.6	44 m/s	8 u
46 m/s	63 m/s	11.2	4	4	4	41 m/s	6 u	45 m/s	6.8	6.2	41 m/s	10 u
55 m/s	65 m/s	12 m/s	7.5	7.7	7.7	46 m/s	7 u	52 m/s	.8	1	42 m/s	6 u
63.5 m/s	59 m/s	12 m/s	6.5	6.7	5	70 m/s	9 u	48 m/s	1.8	1.2	40 m/s	9 u
58 m/s	57 m/s	10.7 m/s	10	9.5	9	63 m/s	14 u	46 m/s	9.5	7.5	36.7 m/s	21 u
58 m/s	64.2 m/s	11.4	8.5	7.0	6.5	44 m/s	9 u	35.7 m/s	3.7	3.7	40 m/s	3 u
60 m/s	63 m/s	16	12.5	12.5	11.5	55 m/s	10 u	50 m/s	1.6	2	40 m/s	16 u
48.2 m/s	72 m/s	8.7	4	3	4	57.5 m/s	6 u	60 m/s	10	9	40 m/s	6 u
58.6 m/s	62.5 m/s	10.9	9	8.0	7.5	52 m/s	3 u	40.7 m/s	1.5	2.8	46.6 m/s	6 u
52 m/s	61 m/s	13.9	12.5	11.3	10.5	46 m/s	18 u	50 m/s	5.2	4.2	39 m/s	20 u
56 m/s	71 m/s	11.2 m/s	12	10.5	9.2	42 m/s	9 u	48 m/s	2.1	1.6	39 m/s	13.5 u
58 m/s	69.2 m/s	11.2 m/s	10	9.7	10	53 m/s	4 u	52 m/s	7.2	6.5	41 m/s	12.5 u
55 m/s	60 m/s	14.3	10.5	9	8.5	52 m/s	5 u	47 m/s	1.6	1.6	42 m/s	8 u
61 m/s	67 m/s	9	13	12.5	12	47.5 m/s	24 u	49 m/s	5.6	5.6	48 m/s	14 u
52.8 m/s	70 m/s	12.7	9.5	8.5	8.5	50 m/s	11 u	37.6 m/s	4	3	41.1 m/s	4 u
58 m/s	54 m/s	10.7 m/s	4	4.5	4.5	50 m/s	10 u	40 m/s	6.6	6.2	38.8 m/s	5 u
55 m/s	66 m/s	13 m/s	8	8.7	8.3	56 m/s	7 u	46 m/s	2.5	2.5	38 m/s	13.5 u
50 m/s	79 m/s	14.8 m/s	14	14.6	14.6	48 m/s	10 u	55 m/s	2.5	1.7	44 m/s	11 u
56 m/s	75 m/s	10.4	8	6.5	6.5	50 m/s	8 u	54 m/s	6.0	5.0	44 m/s	36 u
64 m/s	56 m/s	12.8	8.5	8.7	6.5	49 m/s	6 u	55 m/s	9.2	9.5	42 m/s	6 u
54 m/s	64 m/s	12	8	6.5	6.5	47 m/s	13 u	38 m/s	3.4	2.6	41 m/s	11 u
60 m/s	64 m/s	12.2 m/s	13	12	12	50 m/s	17 u	53 m/s	7	7	43 m/s	12 u
67.6 m/s	70 m/s	14.2	10	10	10	55 m/s	11 u	48.6 m/s	4	4	50 m/s	11 u
61 m/s	64 m/s	11.2	11.3	10.5	9.5	50 m/s	6 u	45 m/s	2.5	2.5	50 m/s	14 u
51 m/s	56 m/s	14	11.5	11.5	11.5	49 m/s	16 u	53 m/s	1.9	1.7	48 m/s	15 u
49 m/s	55 m/s	13	14.5	13.5	13.3	46 m/s	6.5 u	47 m/s	3.05	3.5	40 m/s	10 u
54 m/s	77 m/s	13 m/s	8.5	7.5	7.5	45 m/s	4 u	46 m/s	6.4	6.4	42 m/s	13 u
54 m/s	66 m/s	12.9	11.5	10	10	61 m/s	12 u	43 m/s	4.4	3.4	45 m/s	12 u
55 m/s	59 m/s	12.1	9	9	9	57 m/s	6 u	45 m/s	8	8	43 m/s	19 u
64 m/s	53 m/s	13.3	8	8.5	7.5	55 m/s	7 u	43 m/s	10.7	9	44 m/s	16 u
54 m/s	51 m/s	14.3 m/s	15.5	15.5	14.5	43 m/s	14 u	45 m/s	10	9.5	44 m/s	7 u
55 m/s	48 m/s	11.3	9.5	8.5	8.5	52.6 m/s	5 u	54 m/s	10	10	43 m/s	7 u
52 m/s	54 m/s	13	13.5	13	13	42 m/s	8 u	47 m/s	7.8	6.6	41 m/s	6.5 u
50.5 m/s	64 m/s	13	11	10.5	10.5	absent	absent	41.7 m/s	3.4	3.0	33 m/s	11 u
57 m/s	70.5 m/s	9 m/s	3.2	2.8	2.0	43.5 m/s	3 u	40.5 m/s	4.8	4.0	35 m/s	11 u
59.5 m/s	55 m/s	12.9 m/s	12	12	6.5	49.8 m/s	5 u	42.5 m/s	4.7	4.7	42 m/s	13 u
51 m/s	40 m/s	14	7.5	8	8.3	48 m/s	7 u	44 m/s	4.4	5.1	45 m/s	7 u
53 m/s	51 m/s	13.5 m/s	9.5	9.0	9.0	40 m/s	4 u	39 m/s	3.2	3.0	31 m/s	3 u
57 m/s	57 m/s	12 m/s	3	3.2	3.2	40.5 m/s	3.5 u	34.5 m/s	2	3.4	33.5 m/s	9 u
57 m/s	55 m/s	10.9	9.5	8.6	6.8	52.2 m/s	6 u	45 m/s	2	2	40 m/s	5 u
56 m/s	59 m/s	10 m/s	5.2	4.4	4.4	55 m/s	4 u	52 m/s	5.6	5.2	42.5 m/s	22 u
56 m/s	78 m/s	14.1 m/s	12	11.5	11	45 m/s	11 u	39 m/s	7.0	6.0	45 m/s	14 u
53 m/s	63 m/s	13.2	12.5	10	10	52 m/s	8 u	47 m/s	7	8	40 m/s	14 u
56 m/s	71 m/s	14.6	2.2	1.8	1.8	56 m/s	9 u	47 m/s	3.7	3	45 m/s	9 u
49 m/s	65 m/s	16.7	11.5	9	9	46 m/s	16 u	47 m/s	2.7	2.1	44 m/s	12 u
56 m/s	55 m/s	13.3	16.5	15.5	14.5	48 m/s	13 u	45 m/s	1.2	1.1	42 m/s	7.5 u
59 m/s	60 m/s	14.4	7	7	7	60 m/s	13 u	47 m/s	5	5	48 m/s	19 u
58 m/s	50 m/s	13	8.5	8.5	7.5	42 m/s	5 u	48 m/s	4.6	6.0	36 m/s	5 u
53 m/s	50 m/s	11.5	10.7	7.5	8	55 m/s	6 u	45 m/s	4	3.8	47 m/s	20 u
57 m/s	72 m/s	14.2	9	9	7.5	48 m/s	5 u	36.9 m/s	2.8	1.0	37.8 m/s	11 u
56 m/s	56.5 m/s	9.5	12	11	11	63 m/s	5 u	55.5 m/s	8.5	7.5	45 m/s	7 u
58 m/s	75 m/s	11.5	5.2	6	4.5	45 m/s	10 u	51 m/s	7.7	6.7	45 m/s	18 u
52 m/s	59.5 m/s	12.5	2.4	2.4	2.2	47.5 m/s	10 u	48 m/s	4.8	4.4	43 m/s	18 u
58 m/s	77 m/s	11.7	8	4.5	3.5	40 m/s	4 u	46 m/s	1.7	1.2	39 m/s	1 u
55 m/s	23.7 m/s	11.8 m/s	8.5	8.5	7.5	51.8 m/s	3 u	44.6 m/s	3.8	3.6	41 m/s	8 u
48 m/s	23 m/s	13 m/s	12.5	12	11.5	40 m/s	4 u	38.3 m/s	1.2	0.5	36 m/s	7 u
58 m/s	64 m/s	14.7 m/s	9.2	11	10	50 m/s	10 u	46 m/s	2.5	2.6	42 m/s	15 u

APPENDIX H. Electrical Values

MOTOR ULNAR MCV Vel	W-E	MCV Vel	E-A	MAP Dura	W	AMPL. E	A	SENSORY VEL.	AMPL.	MOTOR PER-ONEAL VEL.	AMPL. Ankle	Knee	SENSORY SURAL VEL.	AMP.
52	m/s	59	m/s	13.6 m/s	9	9	8.5	48 m/s	10 u	47 m/s	5	5	38 m/s	15.5 u
47	m/s	75	m/s	11.5 m/s	12.5	12.4	12.4	42 m/s	5 u	41 m/s	1.9	1.4	38 m/s	6 u
51	m/s	60	m/s	15.7	8	8	8	46 m/s	9 u	44 m/s	2.3	1.9	41 m/s	13.5 u
49	m/s	58	m/s	13.6	12	12	10	50 m/s	9 u	43 m/s	4.8	4.6	45 m/s	10 u
57	m/s	52	m/s	13.2	6.5	6.5	6.5	45 m/s	10 u	48 m/s	9	—	40 m/s	19 u
72.5	m/s	61.3	m/s	13.3	6.5	7	7	62.5 m/s	4 u	47 m/s	6	5	40 m/s	19 u
55	m/s	63.5	m/s	12 m/s	12	12	12	63.7 m/s	12 u	44.5 m/s	11.5	10.7	40.7 m/s	15 u
57	m/s	73	m/s	13.8	9	9	9	55 m/s	6 u	46 m/s	1.5	1.3	42 m/s	10 u
61	m/s	67	m/s	12.8	13.5	12.5	12.3	46 m/s	6.5 u	44 m/s	3.2	2.8	39 m/s	12 u
54	m/s	57	m/s	11	8	7.5	7.5	50 m/s	7 u	41 m/s	1.1	1.1	42 m/s	6 u
53	m/s	64	m/s	9.1	10	10	9	55 m/s	14 u	50 m/s	2.8	2.5	42.5 m/s	8 u
50	m/s	57	m/s	11.5	12	8	9	53 m/s	13 u	44.5 m/s	9	7.5	41.5 m/s	6 u
53	m/s	50	m/s	14	8.5	10	10.5	46 m/s	6 u	48 m/s	5.4	4.9	42 m/s	8.5 u
56	m/s	57	m/s	12	10	10	10	52 m/s	15 u	50.5 m/s	2.5	2.5	36.8 m/s	5 u
48.2	m/s	71.5	m/s	11.4	5	6	5.5	57.5 m/s	6 u	43.5 m/s	1	1	41 m/s	34 u
50	m/s	61	m/s	11.9	12	11	10.5	52 m/s	10 u	38 m/s	3.8	3.2	40 m/s	24 u
58	m/s	57.5	m/s	12	10	9.5	9.5	45.8 m/s	9 u	39.3 m/s	7.5	7	40 m/s	9 u
58	m/s	63	m/s	12.3	11.5	11	10.7	57 m/s	7.5 u	49 m/s	14	13.5	40 m/s	12.5 u
58	m/s	63	m/s	17	9.8	10	9.6	44 m/s	6 u	41 m/s	7.8	7.3	44 m/s	6.5 u
57	m/s	49	m/s	13.2	7.5	7	6.5	54 m/s	14 u	46 m/s	8	6	42 m/s	8 u
56	m/s			14.7	12	11.5		41 m/s	13 u	48 m/s	3.4	2.9	54 m/s	11 u
49	m/s	61	m/s	12.5	8	7.5	6	46 m/s	5 u	43 m/s	1.7	1.6	38 m/s	9 u
57	m/s	50	m/s	13.2	11.5	12	10.7	47 m/s	4 u	55 m/s	6.9	5.4	47 m/s	15.5 u
54	m/s	66	m/s	14.3 m/s	8.5	8	8	50 m/s	14 u	47 m/s	3.8	3.8	43 m/s	12 u
56	m/s	62	m/s	9.7 m/s	12.5	12	10	52 m/s	7 u	47 m/s	12.5	12.5	37 m/s	12 u
55	m/s	70	m/s	13.7 m/s	10	10	10	50 m/s	4 u	44 m/s	3	2	43 m/s	8 u
59.5	m/s	69	m/s	14.3 m/s	15	13.8	13	51 m/s	24 u	47 m/s	9.2	8.5	44 m/s	11.5 u
52	m/s	73	m/s	12.2	10	11	10.5	50 m/s	8 u	50 m/s	10.5	9.5	48 m/s	6.5 u
51.8	m/s	55.1	m/s	10.8	11.5	13.5	13	47.8 m/s	6 u	46.7 m/s	9.5	8.0	40 m/s	3 u
61	m/s	58	m/s	21 m/s	12.5	12	12.5	50 m/s	14 u	42 m/s	1.3	1.6	45 m/s	10 u
53	m/s	65	m/s	10.3	9.5	9	9.5	55 m/s	6 u	47 m/s	2.5	2.4	50 m/s	17 u
54	m/s	61	m/s	11.3	7.5	5	5	52 m/s	8 u	44 m/s	6	4.3	38 m/s	8 u
54	m/s	41	m/s	16.7 m/s	11.7	11.3	11.5	57 m/s	5 u	66 m/s	2	2	41 m/s	10 u
58.6	m/s	70	m/s	12.1	15	15	14	57.8 m/s	10 u	45.9 m/s	8.5	7.5	42.4 m/s	6 u
58	m/s	85	m/s	13.1	6.5	6.5	6.0	55 m/s	5 u	43 m/s	5.7	5.7	35 m/s	12 u
52	m/s	63	m/s	9.9	10	10	10	55.5 m/s	8 u	49 m/s	3.8	3.6	50 m/s	15 u
58	m/s	49	m/s	14 m/s	17	15	13	42 m/s	3 u	37 m/s	0.8	0.75	38 m/s	3 u
58	m/s	70	m/s	13.4 m/s	13.5	12	12	52 m/s	8 u	44.6 m/s	2.0	2.6	43 m/s	10 u
47.5	m/s	48	m/s	15.3	6	5	5	50 m/s	5 u	45.5 m/s	3.6	3.6	43 m/s	14 u
47	m/s	66	m/s	10.9	6.5	6.5	6.5	52 m/s	6 u	38 m/s	5.6	4.0	43 m/s	4 u
56.7	m/s	57.5	m/s	9.5	14	14	13.5	60.5 m/s	9 u	45.9 m/s	7	7	48.2 m/s	7 u
49	m/s	48	m/s	12.4 m/s	6.5	5	5	52 m/s	4 u	44		7.5	7.5 35 m/s	8 u
48	m/s	57	m/s	15.5 m/s	8.5	8.2	8.6	45 m/s	7.5 u	47 m/s	4.6	5.3	42 m/s	9 u
56	m/s	55	m/s	13.2 m/s	8.5	8	8	46 m/s	5 u	42 m/s	2.1	1.2	42 m/s	13 u
54	m/s	70	m/s	10.2 m/s	7	6	6	52 m/s	9 u	46 m/s	7.0	6.5	40 m/s	2 u
53	m/s	64	m/s	13 m/s	16	16	15	41 m/s	3 u	45 m/s	2.5	4.2	34 m/s	6 u
64	m/s	67	m/s	14.8 m/s	8.5	8.5	8.0	50 m/s	10 u	47 m/s	3.8	2.8	42 m/s	18 u
56	m/s	47	m/s	14.2 m/s	9	8.5	8.7	52 m/s	2 u	43 m/s	8	8.5	47 m/s	16 u
61	m/s	60.5	m/s	13.9	15.5	15.5	15.5	48 m/s	8 u	43 m/s	8.8	7.8	42 m/s	13 u
58	m/s	67	m/s	12 m/s	7.6	6.6	6	78 m/s	13 u	48 m/s	4.5	4.7	56 m/s	9 u
52	m/s	78	m/s	15.3	13	10	12	48 m/s	8.5 u	42 m/s	1.7	1.6	44 m/s	10 u
48	m/s	70	m/s	10 m/s	13.5	12	12	52 m/s	10 u	50 m/s	12.5	11.5	45 m/s	12 u
55.8	m/s	53	m/s	9.6 m/s	10	10	9.5	57.8 m/s	12 u	45.8 m/s	5.4	5.4	43.7 m/s	6 u
60	m/s	62	m/s	17.4 m/s	8	7.5	7.5	48 m/s	9 u	46 m/s	7.5	6.5	42 m/s	13 u
53	m/s	61	m/s	13.1	15	15	14	45 m/s	18 u	50 m/s	10 mc	10 mc	42 m/s	16 u
53	m/s	66	m/s	9	10	10.5	10	48 m/s	7 u	43 m/s	5.8	5.8	39 m/s	10 u
50	m/s	62	m/s	10.3 m/s	13	12	12	54 m/s	7 u	40 m/s	6.	5.6	43 m/s	16 u
54	m/s	53	m/s	11	10	7	6.5	54 m/s	4 u	44.5 m/s	4.8	4.8	43 m/s	9 u
54.5	m/s	60	m/s	12.9 m/s	13	7.6	6.8	56 m/s	8 u	53.2 m/s	6	5.4	41 m/s	4 u
54	m/s	71.6	m/s	14 m/s	8.5	8.5	7.5	47.9 m/s	11 u	45.8 m/s	7.4	6.4	42 m/s	19 u
57	m/s	53	m/s	15.7 m/s	10.5	11.5	11	53 m/s	5.5 u	42 m/s	3.2	2.9	44 m/s	12 u
52	m/s	53	m/s	10.8 m/s	9	8	7	46 m/s	11 u	52 m/s	3.1	2.5	40 m/s	3.5 u

APPENDIX I. Normal Values

ULNAR
- *SENSORY*
  - *VELOCITY* = (50-70) M/S
  - S.A.P. AMPLITUDE = (8-28 uV)
- *MOTOR*
  - *VELOCITY*
    - Upper Arm = (52.8-74.0) M/S
    - Fore Arm = (47 -65.4) M/S
  - M.A.P. AMPLITUDE = (5.6-20.8) mV

COMMON PERONEAL
- *MOTOR*
  - *VELOCITY*
    - Leg = (41-59) M/S
  - M.A.P. AMPLITUDE = (2.2-14.8) MV

SURAL
- *SENSORY VELOCITY* = (40-54.7) M/S
- *S.A.P. AMPLITUDE* = (6-42 uV)

APPENDIX Ja. ASARCO Employee Record

1967—142 EMPLOYEE'S WORK RECORD

Key	Seniority or Date Hired	Occupation	Foreman	Rate	Day Went to Work	Left	Key	Remarks

MILITARY AND DRAFT STATUS RECORD

Branch of Service Army		2	Years in Service
Rank Sp/4	Special Awards		
Draft Status	Local Board		Serial Number ER 56380384

VACATION AND LEAVE OF ABSENCE RECORD

From	To	Reason	From	To	Reason	From	To	Reason
ASARCO HEALTH PLAN:								

Key E = Employed; DR = Drafted; O = Laid Off; Q = Quit; T = Transferred; R = Rehired; D = Discharged; N = Dropped

APPENDIX Jb. ASARCO Employee Record
APPENDIX Jb-Tacoma Plant

URINARY ANALYSES—METALS

Last Name	First Name	Initial	Soc. Sec. No.	Plant No.

	ELEMENT—Microgram/Liter						
Date	As	Pb	Hg	Sb	Se	Cd	Department